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REVIEW

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Prostate cancer microenvironment: multidimensional regulation of immune cells, vascular system, stromal cells, and microbiota

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Abstract

Background Prostate cancer (PCa) is one of the most prevalent malignancies in males worldwide. Increasing research attention has focused on the PCa microenvironment, which plays a crucial role in tumor progression and therapy resistance. This review aims to provide a comprehensive overview of the key components of the PCa microenvironment, including immune cells, vascular systems, stromal cells, and microbiota, and explore their implications for diagnosis and treatment.

Methods Keywords such as "prostate cancer", "tumor microenvironment", "immune cells", "vascular system", "stromal cells", and "microbiota" were used for literature retrieval through online databases including PubMed and Web of Science. Studies related to the PCa microenvironment were selected, with a particular focus on those discussing the roles of immune cells, vascular systems, stromal cells, and microbiota in the development, progression, and treatment of PCa. The selection criteria prioritized peer-reviewed articles published in the last five years, aiming to summarize and analyze the latest research advancements and clinical relevance regarding the PCa microenvironment.

Results The PCa microenvironment is highly complex and dynamic, with immune cells contributing to immunosuppressive conditions, stromal cells promoting tumor growth, and microbiota potentially affecting androgen metabolism. Vascular systems support angiogenesis, which fosters tumor expansion. Understanding these components offers insight into the mechanisms driving PCa progression and opens avenues for novel therapeutic strategies targeting the tumor microenvironment.

Conclusions A deeper understanding of the PCa microenvironment is crucial for advancing diagnostic techniques and developing precision therapies. This review highlights the potential of targeting the microenvironment to improve patient outcomes, emphasizing its significance in the broader context of PCa research and treatment innovation.

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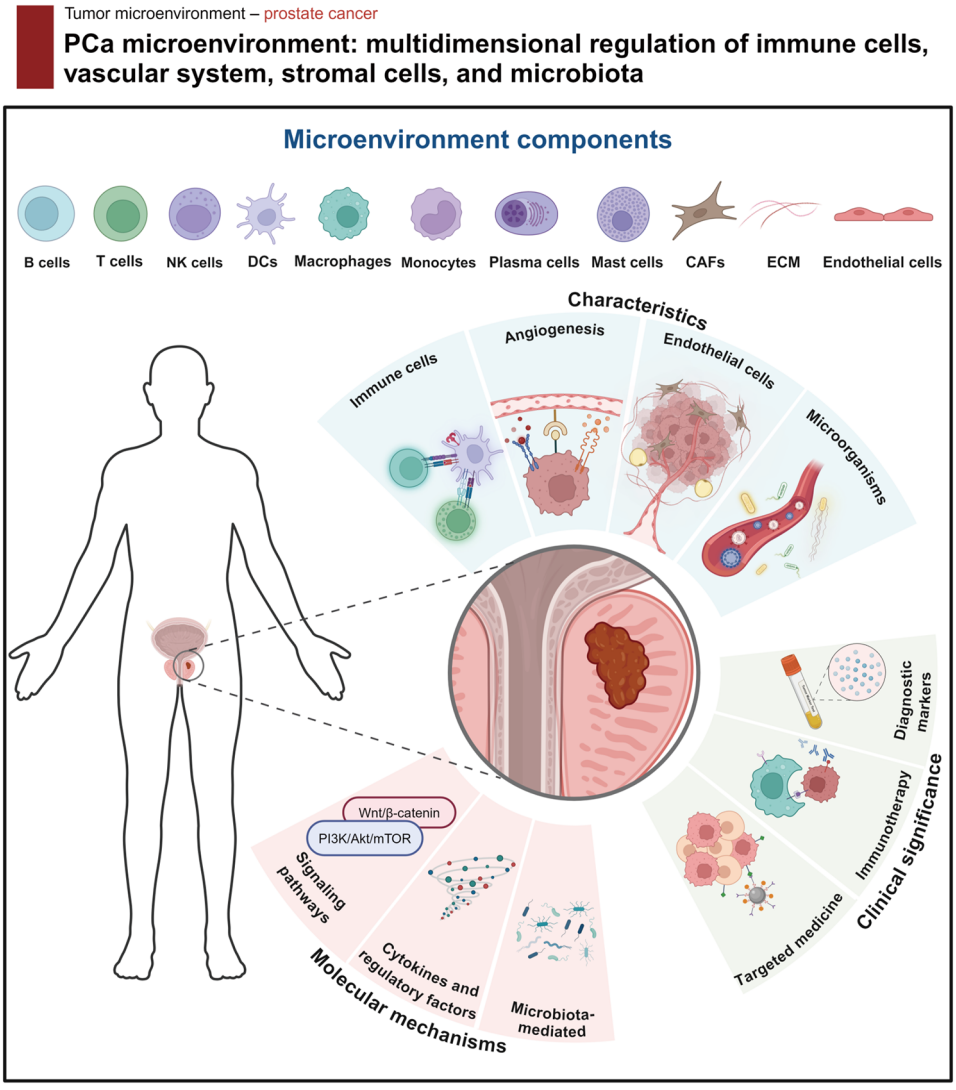
Graphical Abstract



Keywords Prostate cancer, Tumor microenvironment, Immune cells, Vascular system, Stromal cells, Microbiota

Introduction

Prostate cancer (PCa) is among the most common cancers in men globally. Global cancer statistics report approximately 1.4 million new cases and 375,000 deaths annually. The incidence of PCa rises significantly in men over 65, severely impacting their health and quality of life [1]. Recent research from China and the United States indicates a rapid increase in PCa incidence among men aged 25–34. Younger men diagnosed with PCa are more likely to develop aggressive forms of the disease, leading to lower five-year survival rates [2]. Metastatic PCa, compared to non-metastatic PCa, is associated with significantly higher morbidity and mortality. Furthermore, many patients with non-metastatic PCa eventually progress to castration-resistant prostate cancer (CRPC) after undergoing androgen deprivation therapy (ADT). CRPC presents greater treatment challenges and is linked to a poorer prognosis and reduced survival outcomes [3]. Over the past few decades, clinical research on PCa has been a focal point in the medical field [4]. The emergence of the Human Genome Project alongside high-throughput technologies has significantly deepened our grasp of PCa's genetic underpinnings, marking a pivotal focus in research endeavors [5, 6]. However, focusing solely on the

genetic level is insufficient to understand the complexity of PCa. There is increasing recognition that studying the PCa microenvironment is crucial for PCa research, and its comprehensive impact is becoming more prominent [7, 8]. PCa is not only caused by genetic mutations but also by interactions with its surrounding microenvironment. The PCa microenvironment comprises multiple components, including immune cells, vascular systems, stromal cells, and microorganisms, which interact to form a highly dynamic and interconnected ecosystem [9–12]. A deep understanding of the structure and function of this complex network is crucial for elucidating the pathogenesis of PCa. In PCa, the tumor microenvironment (TME) exhibits astonishing levels of hierarchy and diversity [13]. The immune cells exhibit diverse types and functions, with specific T lymphocyte subsets essential for immune surveillance and anti-tumor responses [14]. The vascular endothelial growth factor (VEGF) family, part of the angiogenesis pathway, closely associates with the tumor's blood supply and nutrient delivery, directly impacting tumor growth and spread [15]. Stromal cells exert an impact on tumor invasion and metastasis through modulation of the extracellular matrix (ECM) [16]. Moreover, the connection between the microbiota and PCa is still developing [17]. The adoption of emerging technologies, such as single-cell sequencing, offers significant potential to uncover the intricate details of the PCa microenvironment [18]. This is essential for gaining a comprehensive understanding of PCa and establishing a robust foundation for the development of future therapeutic strategies (Fig. 1).

The clinical significance of the microenvironment in diagnosing, treating, and predicting the prognosis of PCa is becoming more prominent [19]. The potential use of microenvironmental biomarkers has become crucial for early diagnosis and treatment monitoring [20]. The tumor immune response is closely linked to patients' survival rates, making immunotherapy a promising approach for PCa treatment [21]. Additionally, targeted drug research on the microenvironment is ongoing, offering more opportunities for precise treatment [22]. Recent advances in PCa treatment, especially those targeting the TME, have introduced new possibilities for precision therapy [23]. Drugs targeting VEGF inhibit angiogenesis in PCa, reshaping the TME to limit cancer growth and metastasis [24]. Programmed cell death-ligand 1 (PD-L1) inhibitors, such as atezolizumab, enhance the immune system's attack on tumors, providing long-term survival benefits for some PCa patients, especially those with treatment-resistant cases [25, 26]. Traditional non-specific chemotherapeutic agents, like cisplatin and 5-fluorouracil, have limited effects on non-essential molecules within the PCa microenvironment and exhibit significant toxicity, leading to suboptimal anti-tumor effects in clinical practice [27, 28]. While these agents can temporarily suppress tumor growth, prolonged use may lead to adaptive changes in tumors, causing resistance, reduced treatment efficacy, or recurrence. Therefore, when formulating individualized treatment plans, it is crucial to consider the PCa microenvironment and the patient's pathological features. Target key factors involved in tumor growth and metastasis while avoiding excessive intervention on non-essential microenvironment components. This approach aims to maximize therapeutic efficacy, minimize unnecessary side effects, and improve patient survival and quality of life. Another significant challenge in precision therapy for PCa is the variability in individual treatment responses. Different patients exhibit varying responses to the same therapeutic regimen, emphasizing the need for personalized treatment strategies. Integrating multi-omics data, including genomics, transcriptomics, and proteomics, enhances our understanding of the molecular mechanisms underlying PCa, leading to more targeted and effective treatments [29]. Looking ahead, research on the PCa microenvironment still encounters numerous challenges. Continuous innovation in technical methods and research approaches will delve deeper into the mysteries of the microenvironment. Overall, this review will explore various aspects of the PCa microenvironment, aiming to provide readers with a comprehensive and clear overview. By gaining a comprehensive understanding of the complexity of the PCa microenvironment, new insights and inspirations are anticipated to enhance future personalized treatment and clinical interventions.

PCa microenvironment characteristics

Relationship between immune cells and the PCa microenvironment

Immune cells in the PCa microenvironment, including T and B lymphocytes, tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), play a critical role [29, 30]. The role of the androgen receptors (AR) in the PCa immune microenvironment is significant. AR signaling regulates immune cells, particularly T cells and natural killer (NK) cells, and has a profound impact on tumor immune surveillance. Studies have shown that AR signaling upregulates PD-L1 expression, weakening the anti-tumor functions of T cells and NK cells, thereby inhibiting the body's immune response against the tumor [31, 32]. Additionally, AR modulates T cell exhaustion, further enhancing the tumor's ability to evade immune surveillance. AR not only directly affects immune cells but also modifies immune-regulatory factors within the TME, promoting the formation of an immunosuppressive environment. Therefore, AR acts as a critical regulator of immune evasion, playing a pivotal role in the progression of PCa.

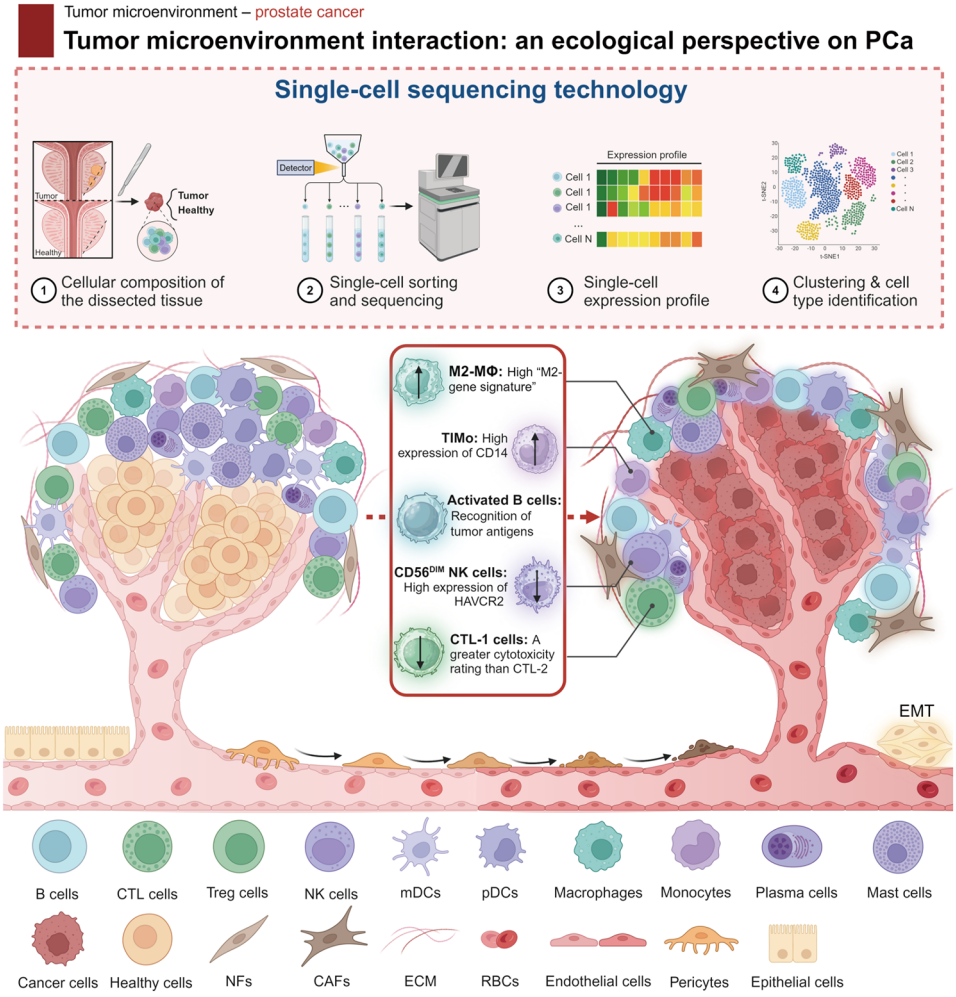


Fig. 1 TME interaction: an ecological perspective on PCa. Single-cell sequencing technology provides a thorough perspective of the PCa microenvironment. The stromal cells, comprising endothelial cells, epithelial cells, pericytes, and CAFs, undergo varying degrees of alterations within the microenvironment of PCa. The M2-macrophages (M2-MΦ) subset of macrophages exhibits significant dynamic changes, underscoring the crucial role of immune regulation in this context. Tumor-inflammatory monocytes (TIMo), as one of the monocyte subpopulations, also demonstrates high levels of variation, further highlighting the immune system's response to PCa. B cells are activated, potentially participating in immune response regulation. However, NK cells activity exhibits a decreasing trend, whereas CTL cells demonstrate significant activity changes, indicating potential distinct roles and regulation of immune cells in responding to PCa

MDSCs are aberrantly activated, immature, and heterogeneous immunosuppressive cells significantly enriched in the PCa microenvironment, impacting PCa development and metastasis [33]. Preclinical in vivo study shows that loss of ARID1A function in mouse models induces MDSCs recruitment by activating the nuclear factor-kappa B (NF-κB) signaling pathway, reduces $CD8^+$ T cells infiltration, creates an immunosuppressive TME, and promotes PCa progression [33]. Clinical studies indicate that MDSCs numbers in the peripheral blood of PCa patients are significantly higher than in healthy donors and negatively correlate with patient survival. Interleukin-23 (IL-23) secreted by MDSCs plays a pivotal role in driving the progression and metastasis of CRPC. Mechanistically, IL-23 inhibition suppresses AR signaling, which in turn reduces the survival and proliferation of PCa cells. Additionally, targeting IL-23 can restore sensitivity to ADT in patients with advanced PCa. Consequently, immunotherapies that block MDSCs recruitment or directly inhibit IL-23 offer promising therapeutic strategies for treating these aggressive and prevalent malignancies [34]. The micro-scale interactions between T lymphocytes and antigen-presenting cells (APCs) in the PCa microenvironment are crucial for understanding PCa development and the anti-cancer immune response [35, 36]. Complex regulatory mechanisms widely recognized influence the differentiation and activation status of T lymphocytes [37, 38]. The importance of APCs in the immune surveillance of PCa has been extensively studied, revealing their key role in tumor immune escape

through intricate interaction networks [36]. These interactions involve signaling networks between APCs and T lymphocytes, as well as interactions with PCa cells. These novel findings deepen our understanding of APCs' functions and provide important clues for designing precise immune therapies targeting the PCa microenvironment. These findings lay a scientific groundwork for the development of more potent cancer treatment strategies and pave the way for further advancements in cancer immunotherapy (Fig. 2).

Subgroups and functions of T lymphocytes

PCa tissues contain various T lymphocyte subgroups, each with distinct roles and functions in the PCa microenvironment. The study of helper $CD4^+$ T (Th) cells, regulatory $CD4^+$ T (Treg) cells, and cytotoxic $CD8^+$ T

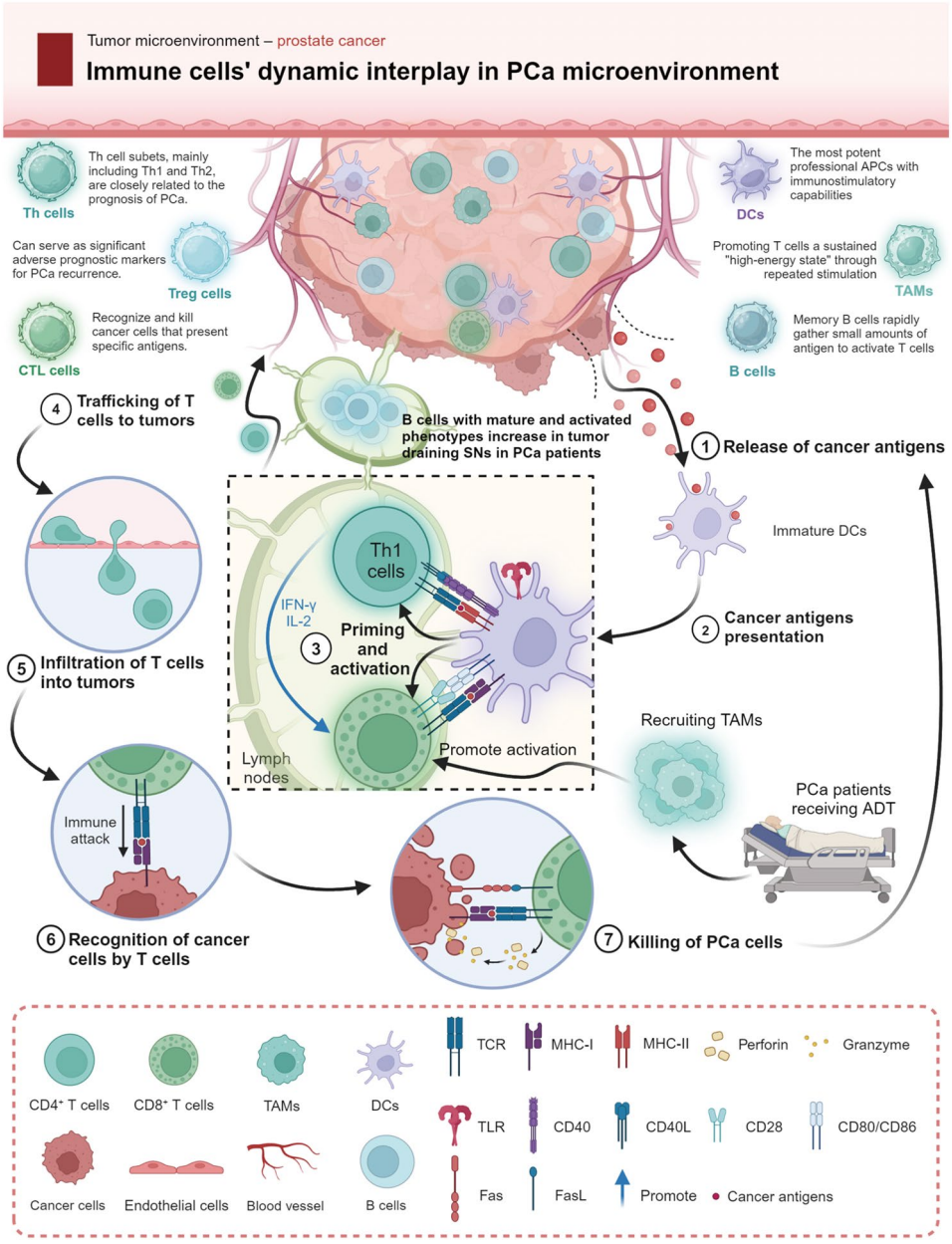


Fig. 2 Immune cells' dynamic interplay in PCa microenvironment. DCs are the most powerful professional APCs with immunostimulatory properties. Despite impaired cellular phagocytic functions, tumor antigens can still be presented to T cells by DC cells. This process involves handling and presenting tumor antigens to T cells, facilitating T cells recognition. $CD4^+$ T cells and $CD8^+$ T cells are then activated and mobilized to infiltrate the PCa site. During this period, PCa patients exhibit an increase in mature and activated B cells within the tumor-draining SNs. Additionally, the immune response in PCa patients who receives ADT is enhanced by promoting the recruitment of TAMs and activating $CD8^+$ T cells. Upon recognizing cancer cells, T cells initiate cytotoxicity against them, promoting the immune system's antitumor response to PCa

lymphocyte (CTL) cells has received significant attention [39–41]. Th1 cells, pro-inflammatory $CD4^+$ T cells, support $CD8^+$ T cells by secreting interleukin-2 (IL-2) and interferon-γ (IFN-γ). An increase in Th1 cells in the PCa microenvironment is closely associated with a favorable prognosis. In contrast, Th2 cells can drive tumor progression, therapeutic resistance, and castration resistance by producing transforming growth factor-β (TGF-β) or prostaglandin E_2 (PGE_2), leading to poor outcomes for PCa patients [42]. Treg cells essential for suppressing inflammatory responses and controlling autoimmunity, are ubiquitous in the PCa microenvironment. They promote tumor development and progression by inhibiting anti-tumor immune responses. For example, Treg cells secrete IL-2 to regulate NK cell homeostasis and function. Treg cells also support PCa cells survival directly through growth factor secretion and indirectly by interacting with stromal cells, such as cancer-associated fibroblasts (CAFs). Thus, infiltrating Treg cells can serve as significant adverse prognostic markers for PCa recurrence [43, 44]. CTL cells recognize abnormal tumor antigens on PCa cells and target them for destruction. After killing PCa cells, CTL cells also inhibit angiogenesis by secreting IFN-γ [45–47]. However, other $CD8^+$ T cells may be inhibited, possibly due to the influence of inhibitory cells and molecules in the microenvironment. This inhibition may lead to functional exhaustion of $CD8^+$ T cells, limiting their anti-tumor effects. Additionally, complex interactions occur among T cells subgroups within the microenvironment [48]. The synergistic effects between $CD4^+$ T cells and $CD8^+$ T cells may critically regulate immune responses. However, the molecular mechanisms of this synergy are not fully understood and require further investigation [49]. The diversity and complexity of T lymphocyte subgroups within the PCa microenvironment necessitate a deeper comprehension of their specific functions, which will enhance the development of more effective immunotherapy strategies for PCa.

APCs

APCs, including dendritic cells (DCs), TAMs, and B cells, are crucial in the immunoregulation of PCa [50, 51]. The immune system's main function is to identify and eliminate abnormal cells, including cancer cells [52]. In this process, APCs present antigens and activate immune cells, but must first be activated. Once activated, DCs absorb, process, and present antigens from PCa cells. These DCs relay this information to nearby lymph nodes, activating naive T cells [53]. Activated T cells then identify and attack PCa cells, resulting in an immune cytotoxic effect [54, 55]. DCs are the most potent professional APCs with immunostimulatory capabilities, and the only APCs capable of activating naive T cells. However, research has demonstrated that PCa cells promote the recruitment of immature DCs to tumor sites by inducing inflammatory chemokine production. This recruitment leads to molecular and signaling alterations in DCs, impairing their antigen-presenting function and ultimately suppressing antitumor immune responses [56]. As the immune response progresses, activated TAMs play a crucial role. They present antigens to engaged T cells, promoting a sustained "high-energy state" through repeated stimulation, enhancing T cells' ability to combat PCa. A Study has shown that after receiving ADT, immune responses are enhanced in PCa patients by recruiting TAMs and activating $CD8^+$ T cells, leading to the death of PCa cells [57]. Additionally, APCs contribute to immune memory formation. Upon activation against PCa, the immune system retains a specific pool of T and B cells. In subsequent encounters with the same antigen, memory B cells rapidly gather small amounts of antigen to activate T cells, resulting in a faster, more effective response [58]. In PCa patients, mature and activated B cells are elevated in the tumor-draining sentinel lymph nodes (SNs), promoting B cell-specific antitumor immune responses [59]. APCs modulate the immune response's magnitude and orientation through the secretion of cytokines like interleukins (IL) and tumor necrosis factor (TNF). This process aids in maintaining immune system equilibrium, ensuring an effective response against PCa cells while preventing excessive immune reactions [60–62].

Relationship between angiogenesis and PCa

Angiogenesis and PCa interaction are heavily researched topics. Recent studies show a strong link between angiogenesis and PCa [63, 64]. The increase in newly formed blood vessels in PCa tissues is closely linked to PCa growth and invasion. These vessels supply nutrients and oxygen to cancer cells and help evade immune surveillance, promoting continuous PCa growth [65]. Additionally, the network of new vessels aids cancer cells metastasis, leading to distant metastatic lesions and affecting PCa prognosis. PCa cells activate multiple angiogenesis-related signaling pathways, such as VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [66–69]. Growth factors and their corresponding receptors are significantly expressed in PCa tissues, promoting new blood vessel formation through the regulation of endothelial cells activities, including proliferation, migration, and lumen formation, among other biological processes. Moreover, studies indicate that oncogene activation and tumor suppressor gene inactivation also contribute to angiogenesis regulation, emphasizing the strong link between angiogenesis and PCa [70]. Extensive research has also uncovered the significant contribution of cytokines and ECM

in the PCa microenvironment during angiogenesis. PCa cells interact with surrounding stromal cells, releasing various cytokines such as interleukin-6 (IL-6), and interleukin-30 (IL-30). These cytokines not only directly promote angiogenesis but also indirectly regulate new blood vessel formation by activating inflammatory responses and altering stromal properties, among other pathways [71, 72]. Moreover, tumor-related angiogenesis is influenced by microenvironmental factors like hypoxia and acidic environments. These factors further increase PCa cells' reliance on angiogenesis [73–75]. A deeper understanding of the relationship between angiogenesis and PCa aids in clarifying PCa's pathogenesis and provides a theoretical foundation for developing targeted anti-angiogenesis therapies. Further research in this field is anticipated to offer new insights and directions for future clinical treatments, potentially enhancing therapeutic options for patients (Fig. 3).

In addition, the AR plays a crucial role in the progression of PCa by regulating angiogenesis. Angiogenesis is a key process by which tumors acquire oxygen and nutrients to promote growth and metastasis, with VEGF serving as a central regulatory factor. Studies have shown that AR signaling can upregulate the expression of VEGF in the TME, thereby promoting the proliferation and migration of endothelial cells and enhancing the formation of

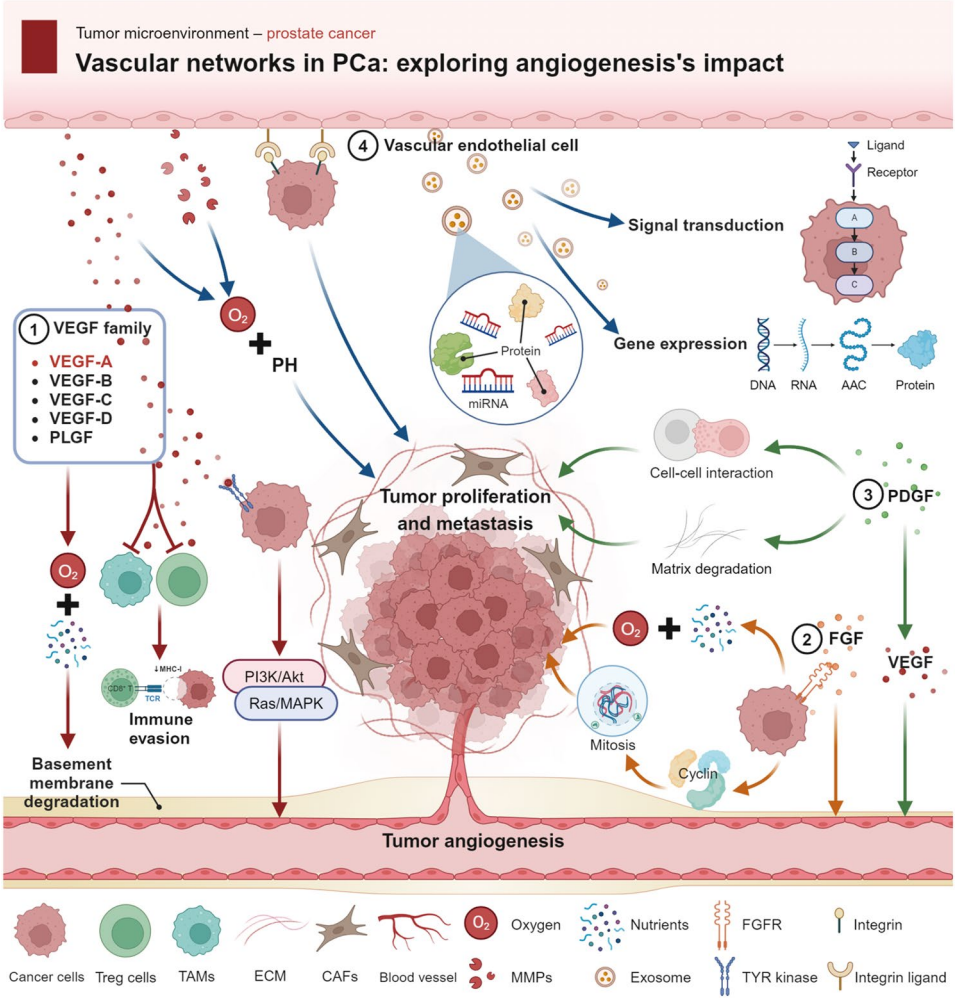


Fig. 3 Vascular networks in PCa: exploring angiogenesis's impact. The VEGF family comprises various subtypes, including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PLGF. VEGF-A binds to TYR kinase receptors, activating signaling pathways such as Ras/MAPK and PI3K/Akt, thereby promoting angiogenesis. VEGF regulates the activity of TAMs and T lymphocytes, impacting the distribution and function of immune cells within the PCa microenvironment and influencing the immune escape mechanisms of PCa cells. VEGF supplies nutrients and oxygen essential for cancer cells invasion and metastasis, influencing critical processes such as cells adhesion and basement membrane degradation, thereby facilitating the migration and spread of PCa cells. The FGF family mediates cells communication through cells surface receptors, promoting cancer cells proliferation and survival, regulating the expression of cells cycle proteins, and influencing cells mitosis and growth. FGF also contributes to angiogenesis, supplying oxygen and nutrients to cancer cells, thus promoting cancer cells growth and spread. Members of the PDGF family drive the spread of PCa cells to surrounding tissues by regulating interactions between cells and degrading the ECM. PCa cells often enhance angiogenesis by producing PDGF, which increases VEGF expression and indirectly regulates vascular development

new blood vessels [76, 77]. Moreover, AR-mediated signaling pathways not only regulate the speed and quality of tumor blood vessel formation but also significantly increase the tumor's blood supply, further driving rapid tumor progression. Specifically, in PCa, AR regulates the expression of VEGF and other angiogenesis-related genes to maintain the vascular network necessary for tumor growth [32]. This mechanism indicates that AR not only controls the proliferation of PCa cells but also accelerates the deterioration of the TME by influencing angiogenesis.

The role of the VEGF family

The VEGF family is identified as the most potent and crucial among the numerous factors involved in angiogenesis. Multiple factors in the PCa microenvironment can trigger VEGF production and subsequent angiogenesis. The VEGF family includes subtypes like vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor-B (VEGF-B), vascular endothelial growth factor-C (VEGF-C), vascular endothelial growth factor-D (VEGF-D), and placental growth factor (PLGF), with varying expression and functions in PCa. This diversity offers extensive evidence for investigating their mechanisms of action [78, 79]. Among these, VEGF-A is extensively studied and binds to the tyrosinase (TYR) kinase receptor, activating signaling pathways like ras-mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), promoting angiogenesis [80]. However, the functions of VEGF and its subtypes like PLGF in the PCa microenvironment are not fully understood, although study suggests their potential roles in regulating tumor angiogenesis, metastasis, and drug resistance [81]. VEGF regulates TAMs and T lymphocytes, shaping immune cell distribution and function within the TME. This modulation directly influences immune cell behavior and the tumor's immune evasion strategies, ultimately impacting overall immune responses [82]. Additionally, the VEGF family is closely associated with tumor cells invasion and metastasis in the PCa microenvironment [83]. VEGF promotes angiogenesis, supplying essential nutrients and oxygen for cancer cells invasion and metastasis. Its influence on critical processes like cells adhesion and basement membrane degradation facilitates favorable conditions for PCa cells migration and spread. Research in this field enhances understanding of PCa development mechanisms, providing new targets and treatment strategies to inhibit tumor invasion and metastasis [67, 81, 84]. Inhibitors targeting the VEGF family are now first-line drugs for PCa treatment [15, 85]. Challenges such as PCa cells resistance and treatment side effects continue. Thus, a thorough understanding of the detailed mechanisms of the VEGF family in the PCa microenvironment can precisely regulate its function, improve treatment effectiveness, and establish more reliable foundations for personalized PCa patient treatment. The significant involvement of the VEGF family in the PCa microenvironment encompasses various aspects like signaling pathways, immune regulation, invasion, and metastasis, offering extensive research evidence for a better grasp of PCa development mechanisms and the development of more effective treatment strategies.

Roles of FGF family

FGF, unlike VEGF, acts on various cell types, directly or indirectly stimulating angiogenesis as a mitogen specific to endothelial cells. The FGF family comprises proteins involved in embryonic development, angiogenesis, wound healing, and cancer progression, exhibiting paracrine, autocrine, or endocrine functions [86]. The FGF family, crucial in regulating signaling pathways, has distinct functions in PCa progression [87, 88]. Binding to PCa cells surface receptors, the FGF family facilitates intercellular communication, promoting PCa cells growth and survival [89]. FGF activation specifically regulates cells cycle protein expression, impacting cells division and growth. This precise regulation is crucial for PCa initiation and progression [90]. Most studies have focused on FGF1 and FGF2 among the several types comprising the FGF family. FGF1 can induce matrix metalloproteinases (MMPs) expression in PCa cells, contributing to malignant progression. FGF2 directly stimulates angiogenesis and plays a role in cancer by inducing cell migration, proliferation, and differentiation [91, 92]. In addition, the FGF family inhibits the transition of PCa to CRPC. Studies have shown that SOX2 is considered to be a regulator of FGF expression, and in CRPC cells, ectopic expression of SOX2 leads to an 18.81-fold increase in FGF levels [93, 94]. This immune evasion promotes PCa development, potentially causing resistance and recurrence. Overall, the diverse roles of the FGF family in the PCa microenvironment offer a new perspective on cancer initiation and progression. Accurately understanding its mechanisms in cells proliferation, angiogenesis, and immune regulation aids in precise PCa interventions and treatments, offering strong theoretical support for future therapies.

The role of the PDGF family

PDGF, a peptide regulatory factor primarily secreted by macrophages, stimulates tissue cell growth. Its role in angiogenesis is weaker than that of FGF and VEGF, suggesting it may not be essential for the initial formation of blood vessels. Under physiological conditions, PDGF resides in platelets and is released upon platelet activation during blood coagulation, stimulating specific cell chemotaxis and growth. The PDGF family regulates tumor growth and metastasis through interactions with PCa cells. Specifically, PDGF family members activate

multiple signaling pathways by binding to receptors on cancer cells surfaces, leading to cancer cells proliferation [95, 96]. A detailed understanding of this mechanism provides new insights into unraveling the molecular regulatory network of PCa cells growth. Additionally, the PDGF family is crucial for PCa invasion and metastasis. PDGF family members promote the spread of PCa cells to surrounding tissues by regulating cell-cell interactions and matrix degradation processes [97, 98]. This discovery deepens our understanding of PCa metastasis mechanisms and provides new targets for intervention in this process. The regulation of angiogenesis in the PCa microenvironment by the PDGF family is of great interest. Tumor cells typically promote angiogenesis by releasing PDGF, which upregulates VEGF expression and indirectly mediates vascular formation. The complex regulatory network of neovascularization provides profound insights for designing more precise anti-angiogenic therapy strategies [99]. In summary, the PDGF family's role in the PCa microenvironment encompasses cells proliferation, invasion, and angiogenesis. A detailed understanding of these mechanisms provides a theoretical basis for future treatment strategies. These research findings provide new perspectives for deepening our understanding of the biological characteristics of PCa and offer strong support for targeted therapy in clinical applications.

Interaction between endothelial cells and PCa cells

Endothelial cells directly influence PCa cells proliferation and invasion by secreting growth factors like VEGF and MMPs [100, 101]. These factors stimulate tumor cells growth and regulate TME acidity, oxygen levels, and consequently, metabolic adaptation and drug sensitivity. Additionally, interactions between endothelial cell surface receptors and those on PCa cells significantly influence tumor biology [102]. Integrin binding between endothelial and PCa cells fosters PCa cells reliance on the microenvironment and activates intracellular signaling pathways, thereby affecting cells migration and infiltration capabilities [103]. Endothelial cells in the PCa microenvironment regulate PCa cells behavior through exosome release [102, 104, 105]. Exosomes carry miRNAs, proteins, and biomolecules that impact gene expression and cells signaling in PCa cells through transport. This offers new insights into the complex interactions between PCa and endothelial cells.

Functions of stromal cells and their impacts on PCa development

Stromal cells are essential for maintaining the structure and function of prostate tissue [106]. They maintain ECM integrity by synthesizing matrix molecules like collagen and elastic fibers, creating a supportive environment for normal prostate cells [107, 108]. However, during PCa development, this supportive function also lays the stromal groundwork for the infiltration and spread of PCa cells, facilitating their invasion into surrounding tissues. In addition to providing structural support, stromal cells also modulate inflammatory responses and immune reactions. The inflammatory state in PCa is considered a key factor in cancer initiation and progression. Stromal cells directly or indirectly influence immune regulation within the PCa microenvironment through the production of inflammatory cytokines, chemokines, and modulation of immune cells activity. These immune regulatory changes may suppress PCa immune responses, contributing to immune evasion in PCa [109, 110]. Stromal cells also contribute to angiogenesis by secreting angiogenesis-related factors such as VEGF, promoting the formation of new blood vessels that supply tumors with oxygen and nutrients. This process is crucial for the growth and metastasis of PCa and provides a potential target for anti-angiogenic therapies.

In this context, CAFs, as one of the most important stromal cells in the TME, play a particularly prominent role in PCa. CAFs promote PCa cell proliferation, invasion, and migration by secreting growth factors, cytokines, and matrix remodeling proteins. AR plays a key role in regulating the function of CAFs. AR signaling directly or indirectly modulates the gene expression of CAFs, altering the secretion of bioactive substances, and thereby promoting tumor progression [111]. For example, AR can upregulate the expression of cytokines such as TGF-β, inducing CAFs to secrete more ECM, which enhances tumor cell invasiveness and drug resistance [112]. Furthermore, CAFs can regulate other components of the TME, such as angiogenesis and immune cell function, through AR signaling, further exacerbating the malignant behavior of the tumor. Therefore, CAFs, as key regulators of the tumor stroma, provide multiple layers of support for PCa development through their interaction with AR signaling.

The presence of stromal cells also significantly impacts the therapeutic response in PCa. Due to their involvement in forming and maintaining the PCa microenvironment, stromal cells may affect the delivery and efficacy of anticancer drugs [22]. Additionally, stromal cells may directly or indirectly influence treatment outcomes by regulating drug sensitivity and resistance in PCa. These findings underscore the importance of considering the multifaceted roles and impacts of stromal cells in the PCa microenvironment when developing treatment strategies for PCa (Fig. 4).

Roles of CAFs and adipocytes

Stromal cells, such as CAFs and adipocytes, are crucial in the PCa microenvironment [113, 114]. CAFs, located primarily in stromal tissue, maintain tissue structure,

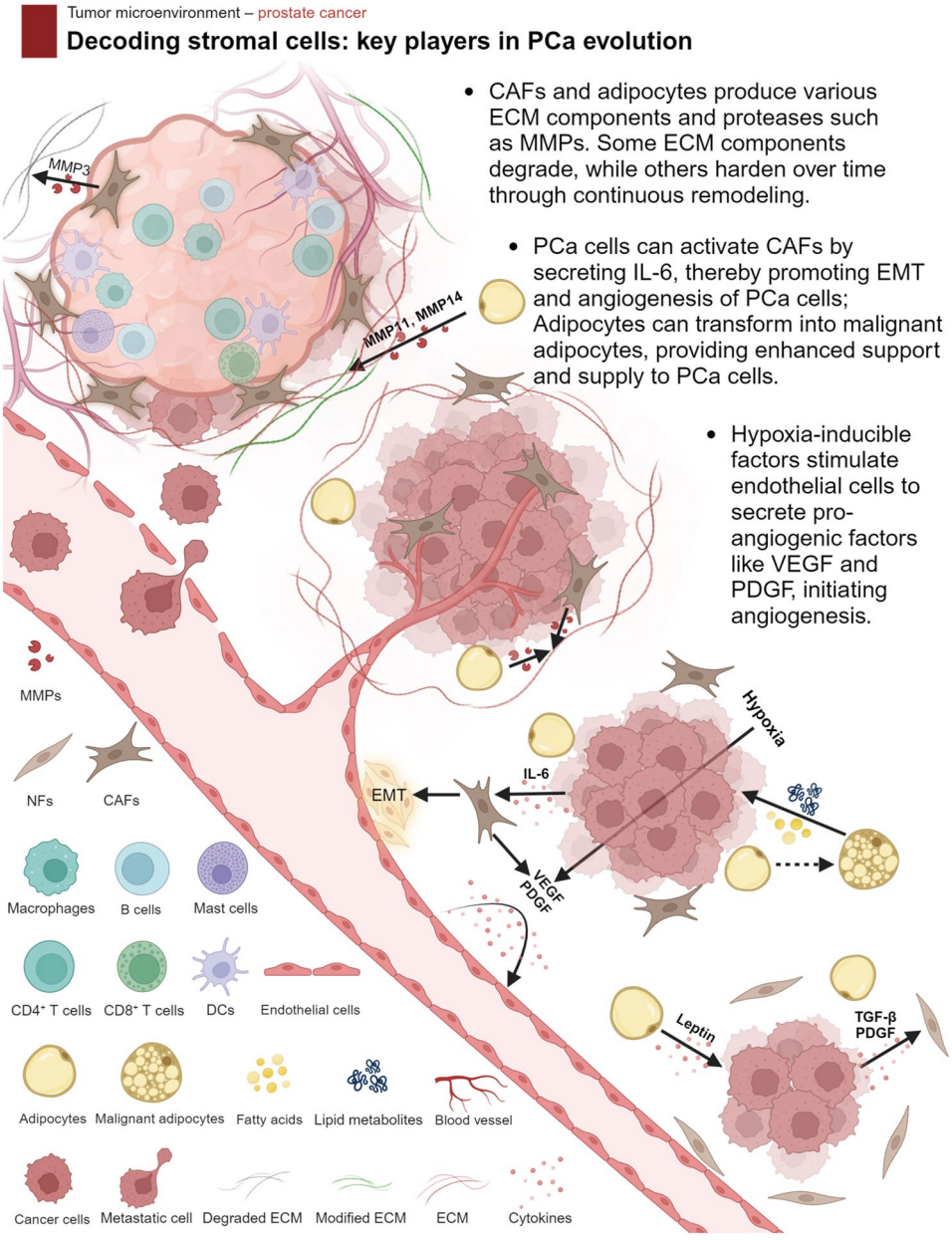


Fig. 4 Decoding stromal cells: key players in PCa evolution. CAFs and adipocytes produce various ECM components and proteases such as MMPs. Some ECM components degrade, while others harden over time through continuous remodeling. PCa cells can activate CAFs by secreting IL-6, thereby promoting EMT and angiogenesis of PCa cells; Adipocytes can transform into malignant adipocytes, providing enhanced support and supply to PCa cells. Hypoxia-inducible factor stimulates endothelial cells to secrete pro-angiogenic factors like PDGF and VEGF, initiating the process of angiogenesis

regulate cell signaling, and participate in cell proliferation and differentiation. Within the PCa microenvironment, CAFs and PCa cells interact, with PCa cells activating CAFs by secreting IL-6. Once activated, CAFs promote the epithelial-mesenchymal transition (EMT) of PCa cells and secrete growth factors that enhance angiogenesis, supplying PCa cells with nutrients and oxygen, thus fostering their growth [115–117]. Recent studies indicate that CAFs exhibit higher levels of autophagy than normal fibroblasts (NFs) and promote the malignant phenotype of PCa through autophagy-related gene 5 (*ATG5*) dependent autophagy [76, 118]. CAFs also influence the immune system's surveillance and clearance of cancer cells by modulating the activity and distribution of immune cells. These changes in immune regulation help cancer cells evade immune surveillance within the host, enhancing their survival and dissemination opportunities. Additionally, adipocytes, another type of stromal cells, contribute significantly to the PCa microenvironment [119]. Adipocytes, primarily located in

adipose tissue, are responsible for storing and releasing fat and regulating energy metabolism [120]. During the progression of PCa, adipocytes can transform within the PCa microenvironment to become malignant adipocytes. This transformation is influenced by various factors secreted by PCa cells and CAFs, which induce changes in the function and phenotype of adipocytes. For instance, the release of inflammatory cytokines and alterations in signaling pathways can lead to the recruitment and activation of adipocyte precursor cells, which then differentiate into malignant adipocytes [121]. Malignant adipocytes release significant amounts of lipid metabolites and fatty acids, providing essential energy and nutrients for PCa cells growth and metastasis [122]. Thus, CAFs and adipocytes in the PCa microenvironment play roles beyond PCa support, involving various mechanisms in tumor growth, dissemination, and immune evasion.

The role of ECM

The ECM's role in the PCa microenvironment has attracted significant attention and is a recent focus of research [123]. The ECM mainly consists of collagen, fibronectin, elastin, and glycoproteins like laminin. Interactions between cancer cells and stromal cells alter ECM components, affecting cancer cell invasion and metastasis [124]. Cancer cells recruit stromal cells like CAFs and adipocytes, which collaboratively remodel the ECM. These stromal cells produce and release various ECM components and proteases, including MMPs. Some ECM components degrade, while others harden over time through continuous remodeling. Increasing evidence shows that ECM stiffening drives PCa growth, invasion, and metastasis. Clinically, malignant lesions are often stiffer than benign tissues. This finding offers novel biomarkers for predicting PCa progression and metastasis. Additionally, ECM stiffening may crucially affect the PCa microenvironment by modulating signaling pathways. Numerous studies have shown that key pathways in CRPC, such as PI3K/Akt and MAPK, are activated by ECM stiffening [125, 126]. The ECM's role in the PCa microenvironment goes beyond traditional support and structure, uncovering complex and diverse functions. These studies enhance our comprehension of ECM's role in the PCa microenvironment and provide general insights for understanding and intervening in PCa microenvironments.

The relationship between microorganisms and PCa

In previous research, microbiologists and cancer researchers have increasingly turned their attention to the biomedical aspects of the relationship between bacteria, viruses, and PCa [17, 127]. Recently, advanced molecular biology and high-throughput sequencing technologies have allowed us to recognize the potentially crucial regulatory role of the microbiota in the etiology and progression of PCa [128]. The relationship between PCa and bacteria has garnered significant attention, particularly in earlier studies that emphasized the potential role of urethral bacteria in PCa development [129]. Nevertheless, recent studies have identified a specific microbial community in prostate tissue, comprising distinct bacterial subgroups [130, 131]. These bacteria may significantly impact PCa development by activating inflammatory pathways, influencing immune responses, or directly interfering with the cells cycle [132]. This finding emphasizes the intricate relationship between bacteria and PCa, offering a fresh perspective for investigating the specific role of prostate microbiota. Simultaneously, viruses are also implicated in the pathogenic mechanisms of PCa [133]. Virus infections have been linked to various cancer developments, with specific interest among researchers in certain viruses found in PCa, such as human papilloma virus (*HPV*), epstein-barr virus (*EBV*), and the human herpes virus (*HHV*) [134–136]. These viruses may contribute to PCa pathogenesis through multiple pathways, such as direct interference with cells genome stability, impact on cells survival signaling pathways, and interaction with the host immune system. Thus, the presence of viruses can significantly impact the pathophysiological processes of PCa. It is important to note that the relationship between microorganisms and PCa remains complex and challenging to research [129, 137]. Future investigations should employ extensive experimental designs and conduct large-scale human studies to substantiate these connections, thereby enhancing our insights into the involvement of microorganisms in the onset and progression of PCa. This not only uncovers potential pathogenic mechanisms of PCa but also establishes a solid foundation for developing new prevention and treatment strategies (Fig. 5).

Despite the increasing focus on the relationship between microorganisms and PCa, the connection between AR and gut microbiota has not been extensively studied. However, recent evidence suggests that AR may indirectly regulate the composition of gut microbiota by influencing the host's immune and metabolic states, thus impacting the development of PCa. Studies indicate that androgen signaling could alter the body's metabolic activities and oxidative defense systems, thereby affecting the diversity and stability of the gut microbiota. For example, AR may influence the immune-metabolic state of PCa patients, which in turn affects the composition of the microbiota and indirectly impacts the tumor's immune microenvironment. Additionally, certain gut microbiota are closely related to the host's hormone levels and can metabolize androgens, further regulating the metabolic environment of both the gut and the tumor [34]. Therefore, the relationship between gut microbiota and AR

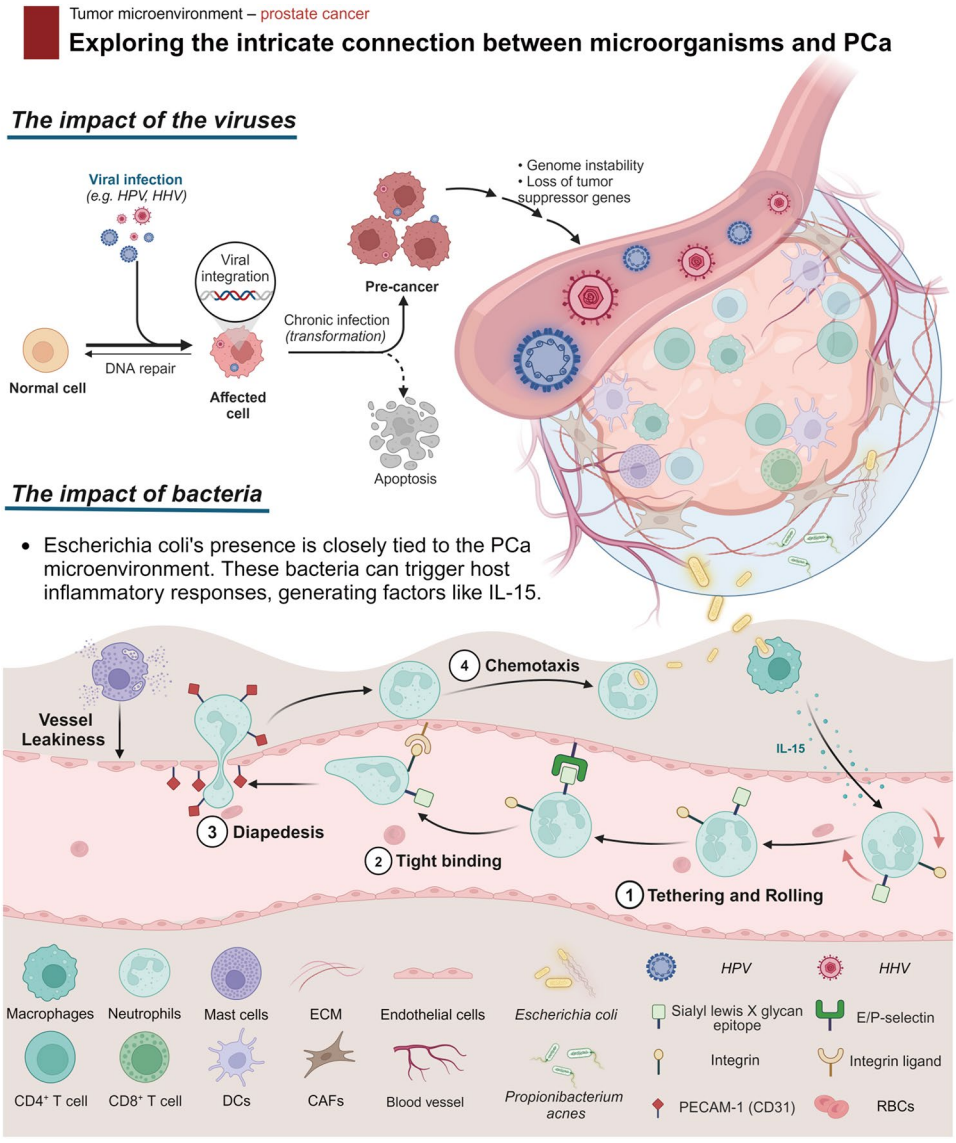


Fig. 5 Exploring the intricate connection between microorganisms and PCa. Upon viral infection, normal cells may undergo integration of the virus into their DNA, resulting in apoptosis or transformation into pre-cancerous cells. Bacterial stimulation elicits inflammatory responses that can activate IL-15, influencing neutrophil activity and impacting PCa progression

offers a new perspective for PCa research, especially in exploring the systemic effects of androgen signaling. Future investigations should focus on further elucidating the interaction between AR and gut microbiota, which will enhance our understanding of the pathological mechanisms of PCa and pave the way for developing new treatment strategies.

The influence of bacteria in the PCa microenvironment

Various bacteria, such as those from the gut microbiota, inhabit prostate tissue, leading scientists to investigate their role in PCa development [138, 139]. Bacteria's presence in the PCa microenvironment can modulate host immune responses. *Propionibacterium acnes* and *Escherichia coli* are common in prostate tissue and closely linked to cancer development. Enrichment of *Propionibacterium acnes* in prostate tissue is linked to PCa development [140–142]. Moreover, *Escherichia coli*'s presence is closely tied to the PCa microenvironment. These bacteria can trigger host inflammatory responses, generating factors like interleukin-15 (IL-15). This process could inhibit PCa development by activating inflammatory pathways [142]. Additionally, inflammatory stress can induce tumor-associated epigenetic alterations, such as histone methylation, acetylation, and DNA methylation. The presence of bacteria in PCa could potentially influence the effectiveness of drug therapy. Several studies indicate that the presence of bacteria might disrupt drug

distribution and metabolism within PCa tissue, thereby potentially impacting treatment efficacy [143–145]. This discovery is crucial for optimizing PCa treatment plans and gaining insights into personalized therapy [146]. Overall, bacteria in the PCa microenvironment could influence cancer development and treatment outcomes via multiple pathways. These findings are valuable not only for basic PCa research but also offer innovative directions for clinical medicine.

Impacts of viruses in the PCa microenvironment

Viruses in the PCa microenvironment have generated significant interest in the academic community [147]. Studies have demonstrated the presence of various viruses in this microenvironment [134, 148]. These viruses display intricate diversity within PCa tissues and affect the host organism at various biological levels. This virus can modulate PCa cell behavior through its impact on inflammation, angiogenesis, and apoptosis pathways [149]. In certain cases, within the PCa microenvironment, *HPV* infection has been detected, potentially influencing the proliferation and metastasis of PCa cells by modifying cell cycle regulation and manipulating host gene expression [150]. Specifically, the E6 and E7 proteins of *HPV* bind to p53 and retinoblastoma (Rb) proteins, respectively, disrupting their normal functions. This disruption subsequently affects cell cycle regulation and alters miRNA gene expression [134, 151]. *HPV* infection may offer a potential mechanism for PCa evasion by suppressing the host's immune response, especially in recognizing and clearing tumor antigens [152]. Moreover, the presence of *HHV* is closely linked to PCa development and can affect tumor growth via immunosuppressive pathways. Complex interactions occur between these viruses and immune responses in the PCa microenvironment. *HHV*'s presence may reduce immune function, impairing the host's response to cancer cells and promoting PCa development. The impact of viruses on PCa treatment is highly significant [135, 136]. In this context, thorough research into virus mechanisms in the PCa microenvironment is anticipated to yield fresh insights for future cancer research and provide more precise clinical management and treatment strategies.

Deciphering molecular pathways within the PCa microenvironment

Roles of signaling pathways

The intricate network of signaling pathways between PCa cells and their microenvironment profoundly influences the tumor's behavior. Activation of the Wnt/β-catenin signaling pathway is closely linked to PCa cells proliferation, invasion, and metastasis [153–155]. Notably, this pathway's activity is closely tied to inflammatory reactions in the PCa microenvironment, emphasizing its role in PCa development [156]. Precise regulation of the Wnt/β-catenin signaling pathway may present novel PCa treatment strategies. Conversely, regulation of the PI3K/Akt/mechanistic target of rapamycin kinase (mTOR) signaling pathway in the PCa microenvironment has garnered significant interest [157]. Overactivation of this pathway in PCa cells correlates with drug resistance and heightened inflammation in the microenvironment. Moreover, PI3K/Akt/mTOR pathway activation directly impacts PCa cells metabolic changes, creating a conducive environment for tumor cells survival [158]. A comprehensive study of this signaling pathway will elucidate cells survival mechanisms and treatment resistance in the PCa microenvironment. Research on PCa microenvironment signaling pathways not only reveals PCa initiation and progression mechanisms but also guides precision therapy development.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway has multiple effects on the TME. Firstly, it significantly influences the number and function of cancer stem cells (CSCs) by regulating their self-renewal and differentiation processes [159]. Activation of this pathway is closely associated with maintaining and expanding PCa stem cells, impacting the tumor's long-term survival and regeneration [160]. Secondly, activation of the Wnt/β-catenin signaling pathway also affects the polarity and migratory ability of PCa cells. By regulating cells adhesion and tight junctions, this signaling pathway influences PCa infiltration and metastasis [154, 161]. In terms of immune regulation, its activation not only inhibits anti-tumor immune responses but may also influence the quantity and activity of tumor-associated immune cells [162]. Abnormal activation of the Wnt/β-catenin signaling pathway may lead to PCa immune escape, reducing immune cells recognition and clearance of PCa cells, providing a potential mechanism for PCa immune escape [163]. Additionally, the Wnt/β-catenin signaling pathway contributes to the regulation of the ECM and angiogenesis in the PCa microenvironment [164]. Its activation may affect the synthesis and degradation of tumor-related stroma, altering the mechanical properties of the TME and cell-cell interactions. In terms of angiogenesis, activation of the Wnt/β-catenin signaling pathway is associated with factors related to PCa angiogenesis, potentially influencing the PCa's blood supply by promoting the proliferation and migration of endothelial cells, affecting the PCa's vascularization [165]. Moreover, researchers found through constructing datasets for primary PCa and benign prostate samples that the Wnt/β-catenin signaling pathway plays an important role, and the ubiquitin conjugating enzyme complex (UBE2C) may be a key node in this signaling pathway [166].

PI3K/Akt/mTOR signaling pathway

The PI3K/Akt/mTOR signaling pathway is a critical cellular signaling cascade that activates Akt protein phosphorylation via PI3K kinase activation, ultimately resulting in mTOR activation [167, 168]. This pathway directly regulates PCa cells metabolism, protein synthesis, and growth, exerting a direct impact on PCa development [169, 170]. Furthermore, the PI3K/Akt/mTOR signaling pathway is closely associated with inflammatory responses in the microenvironment of PCa. Aberrant activation of this pathway may lead to the release of inflammatory factors, inducing inflammatory responses in the TME, thereby affecting immune cells infiltration, activity, and significantly influencing PCa immune evasion [171]. Research has shown that the PI3K/Akt signaling pathway can promote the release of exosomes and upregulation of PD-L1 expression in PCa cells, which greatly alters the immunosuppressive state and affects macrophage polarization [172]. Additionally, the PI3K/Akt/mTOR signaling pathway directly participates in regulating angiogenesis by modulating VEGF and other molecule expressions, thus affecting PCa vasculature and impacting PCa growth and metastasis [83, 173]. The PI3K/Akt/mTOR signaling pathway also contributes significantly to the development of treatment resistance in PCa. Research indicates that as PCa progresses to a resistant stage, it may shift from relying on AR signaling to dependence on the PI3K/Akt/mTOR pathway. Hyperactivation and dysregulation of this pathway are linked to increased tumor aggressiveness [174, 175]. Thus, targeting the PI3K/Akt/mTOR pathway may offer a promising therapeutic strategy to overcome resistance in PCa. Therefore, attaining a thorough comprehension of the PI3K/Akt/mTOR signaling pathway's involvement in the microenvironment of PCa is anticipated to unveil novel insights and therapeutic targets for PCa management.

Cytokines and regulatory factors

The TNF family members play diverse roles in immune response regulation and cells survival [176]. Studies show tumor necrosis factor-α (TNF-α) is overexpressed in PCa, closely linked to tumor development and microenvironmental inflammation [177, 178]. Further investigation is needed to determine the specific roles of tumor necrosis factor-β (TNF-β) and factor associated suicide ligand (FasL) in the PCa microenvironment. Precise cytokine regulation can significantly impact tumor growth, infiltration, and metastasis. Transcription factor regulation is crucial for tumor development in the PCa microenvironment. NF-κB is a critical transcription factor within the regulatory network of PCa [179, 180]. Thus, studying NF-κB's role and regulatory network in the PCa microenvironment is crucial for understanding tumor pathogenesis and identifying new therapeutic targets.

TNF family

The TNF family's extensive involvement in the PCa microenvironment has significant implications for tumor development and treatment response [181]. This is a family of multiple cytokines that play important roles in various biological processes such as cell proliferation, differentiation and apoptosis, immune regulation, inflammatory response, angiogenesis, and invasion. Certain TNF family members can directly regulate PCa cells proliferation by activating some specific signaling pathways. TNF-α is an important member of the TNF superfamily, with a wide range of biological functions and important roles in PCa [182]. TNF-α can induces proliferation and invasion of PC3 cells through activation of PI3K/Akt and NF-κB signaling pathways [183]. Moreover, some TNF family members regulate cells apoptosis, affecting the survival status of PCa cells [184]. Fas/APO-1/CD95 is a member of the TNF receptor superfamily, which can induce tumor cell apoptosis. In the PCa microenvironment, the Fas signaling pathway has complex interactions with other important tumor signaling pathways, which further regulates the survival, proliferation, and apoptosis of PCa cells [185]. Research has shown that Fas induces apoptosis in DU145 cells by activating JNK and MAPK, which in turn affect the downstream BCL2 family [186]. These findings highlight the critical role of the TNF family as key regulators of cells fate in the PCa microenvironment. Recent studies have shown that some TNF family members play crucial regulatory roles in immune cells infiltration and activation [187, 188]. These members such as TNF-α and TNF-related apoptosis-inducing ligand (TRAIL) may influence PCa's immune evasion by modulating the activity of immune cells like T cells and NK cells [189, 190]. Additionally, the TNF family regulates the expression of immune checkpoint molecules, affecting PCa's sensitivity to immunotherapy [191]. TNF family members also play a significant role in angiogenesis, PCa invasion, and metastasis in the PCa microenvironment. In the TME of PCa, TRAIL plays an important role, not only affecting immunity, but also regulating invasion and metastasis [192, 193]. Recent research shows that certain TNF family members directly affect PCa's blood supply and growth by regulating vascular endothelial cells function and angiogenesis-related signaling pathways [194, 195]. These insights deepen our understanding of the TNF family's role in PCa's microenvironment.

Transcription factors

Transcription factors in the PCa microenvironment profoundly regulate PCa development through multiple mechanisms [196, 197]. NF-κB participates in regulating inflammation and modulates key processes such as cells survival, proliferation, and invasion in PCa occurrence

and progression [198, 199]. Activity regulation of NF-κB may be closely associated with inflammation status, cell-cell interactions, and immune escape in the PCa microenvironment. In terms of inflammatory status in the PCa microenvironment, NF-κB can regulate the expression of various pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β [200, 201]. The excessive activation of NF-κB can maintain and exacerbate the inflammatory state, and inhibiting the activity of NF-κB may be a potential therapeutic strategy that can slow down or prevent the progression of PCa. In addition, NF-κB can affect the escape of tumor cells from the immune system. It can promote the expression of PD-L1, and the binding of PD-L1 to programmed cell death protein-1 (PD-1) receptor can inhibit the activity of T cells, thereby helping tumor cells escape immune surveillance [32, 202]. Furthermore, transcription factors regulate PCa cells surface antigen expression, affecting PCa cells recognition efficiency by the immune system and modulating PCa immune escape [203]. Certain transcription factors can interact with proteins related to cells cycle regulation, such as cyclin-dependent kinases (CDKs) and cyclin-dependent kinase inhibitors (CKIs), to regulate PCa cells cycle progression [204, 205]. Transcription factors also directly regulate DNA replication and chromosome segregation, thus directly influencing cells proliferation [206]. Specific transcription factors can directly intervene in immune cells function in the PCa immune microenvironment [207–209]. This involves transcription factors regulating immune cells surface receptors, co-stimulatory molecules, and cytokines, impacting immune cells activation, proliferation, and effector functions. Specific transcription factors directly regulate genes related to angiogenesis, including VEGF and basic fibroblast growth factor (bFGF). This regulation influences oxygen and nutrient supply to PCa cells, affecting PCa growth and invasion [65, 210, 211]. In summary, transcription factors profoundly impact PCa microenvironment regulation through direct involvement in cells cycle regulation, immune modulation, angiogenesis, and nutrient supply, among other mechanisms.

Microbiota-driven molecular pathways

Bacterial mediated

Recent research indicates that the composition of gut bacteria can impact the efficacy of tumor immunotherapy [212]. In germ-free or symbiotic eradication conditions of the gut microbiota, the efficacy of immunotherapy drugs like PD-L1 inhibitors are significantly reduced in various animal tumor models. Human study has also shown that abnormal gut microbiota composition can lead to immune checkpoint inhibitor (ICI) resistance in epithelial cells [213]. In their study involving 23 patients with metastatic castration-resistant prostate cancer (mCRPC) receiving enzalutamide treatment, Peiffer et al. used fecal sequencing of gut microbiota. They found that although there was no significant difference in gut microbiota diversity between responders and non-responders, responders had higher levels of Streptococcus salivarius in their feces compared to non-responders. Oral Streptococcus salivarius levels were not linked to response status [214]. Furthermore, muciniphila has shown a correlation with immune therapy response in PCa, exhibiting increased abundance in the fecal samples of PD-1 inhibitor responders. Conversely, its levels are reduced in mCRPC. This suggests a novel approach to boosting immune therapy response through fecal transplant from responders, although more research is needed to confirm its clinical viability [215]. Recent studies have shown that the bacterium *Ruminococcus* is significantly enriched in patients with CRPC and is associated with phospholipid metabolism [216, 217]. These findings are crucial for optimizing PCa treatment plans and understanding the potential for personalized therapy. Furthermore, current research on immune therapy in PCa and the microbiota predominantly centers on gut microbiota, with few studies investigating microbiota in the prostate or urogenital tract, which could also influence immune therapy effectiveness in PCa. Thus, future research should investigate the connection between these microbiota and immune therapy.

Recent studies have indicated that gut commensal bacteria may play a significant role in the production and metabolism of androgens within the body, even in patients undergoing ADT. For example, some research has found that certain gut microbiota can produce androgens by metabolizing precursor substances, thereby affecting the host's hormone levels and the immune microenvironment of tumors [218, 219]. The androgen-producing capabilities of these bacteria may significantly impact the effectiveness of ADT and the progression of the disease. Therefore, exploring the mechanisms of androgen production and secretion by gut microbiota in the context of ADT is crucial for a comprehensive understanding of their influence on PCa. Future research should focus on elucidating the role of gut commensal bacteria in androgen metabolism in ADT patients to reveal their potential impact on PCa development. This will not only enhance our understanding of the pathological mechanisms of PCa but may also provide important insights for the development of new therapeutic strategies.

Virus mediated

HPV *HPV* is a group of viruses with pleomorphic characteristics that can infect various parts of the human body, such as the skin, reproductive tract, urethra, and respiratory tract, leading to tissue proliferation, verrucous epi-

thelial lesions, malignant tumors, etc [220]. According to statistics from Russo et al. in 2018, there were 98 studies from 1990 to 2015 on the association between *HPV* infection and the incidence of PCa, involving over 9,000 participants, with 3,939 individuals in the experimental group and 5,683 in the control group [221]. This study primarily focused on the association between *HPV*-16 and *HPV*-18 infections and PCa. Meta-analysis results showed that *HPV*-16 infection increased the average odds ratio (OR = 1.61) of PCa risk, while *HPV*-18 infection had a relatively lower average odds ratio (OR = 1.20) of PCa risk. From the data results, the association between *HPV*-16 and PCa appears more pronounced, while the relationship between *HPV*-18 and PCa may require more experimental data for verification.

EBV *EBV* was initially discovered and isolated in biopsy samples from Burkitt's Lymphoma patients in 1964. Studies have demonstrated notable differences in anti-apoptotic factors (e.g., survivin and Bcl-2) and tumor suppressor factors (e.g., p53 and Rb) among *EBV*-infected PCa samples, highlighting the potential influence of *EBV* on PCa development [222, 223].

HHV The *HHV* comprises herpes simplex virus type-1 (*HSV-1*) and herpes simplex virus type-2 (*HSV-2*), representing typical herpesvirus types [224]. Acute herpes simplex virus (*HSV*) infection causes vesicular dermatitis and can lead to inflammations and reproductive system infections. Studies show that the oncolytic *HSV*, combined with the PI3K inhibitor BKM120, synergistically enhances the eradication of PCa stem-like cells [225]. Major discoveries about *HSV* and new PCa therapies present novel opportunities for PCa diagnosis and treatment, rendering related research a recent hot topic [226].

The role of bacteria and viruses in the PCa microenvironment entails intricate molecular mechanisms significantly influencing tumor progression and treatment response. Uncovering these mechanisms mediated by bacteria and viruses aids in enhancing the comprehension of PCa pathophysiological processes, offering fresh perspectives for designing future targeted therapy and immunotherapies (Table 1).

Significance of PCa microenvironment in clinical practice

PCa diagnosis

In the field of PCa diagnosis, research on microenvironmental markers primarily involves multiple aspects, including genetic variations, ECM, extracellular vesicles, and metabolites [227]. Identifying specific TME biomarkers is crucial in diagnosing PCa. These biomarkers encompass various types, including ECM proteins (e.g., Collagen type VII, MMP-1, MMP-2, MMP-7, MMP-9, MT1-MMP, CUL4B) indicating tumor invasiveness [228–230]; CSCs markers (e.g., BTF3, Skp2, BMI1, Sox2, ALDH1A1, ALDH1A3, ACK1, TNK2) influencing PCa recurrence and treatment resistance [231–234]; transcription factors (e.g., NF-κB) associated with PCa initiation and progression [235]; IL (e.g., IL-6, IL-8) pivotal in PCa inflammation and progression [236, 237]; growth factors (e.g., VEGF, FGF1, FGF2, FGF6, FGF8, TGF-B, PDGF) critical in tumor immune evasion and microenvironment regulation [238–240]; immunomodulators (e.g., PTX3, COX-2) aiding in assessing tumor immune escape and potential targets for ICI therapy [241, 242]; angiogenic stimulators (e.g., Ang-1, EGF, TGF-α) significant in modulating the TME and promoting growth [243, 244]; chemokines (e.g., CXCL12) pivotal in tumor cell migration and metastasis [245]; and glycoproteins (e.g., THBS4) promoting tumor progression via the PI3K/Akt pathway [246]. Detecting these biomarkers aids in early PCa diagnosis and predicts disease progression and patient prognosis, offering crucial insights for personalized treatment strategies. In-depth study of genetic variations, precise analysis of specific genes in the PCa microenvironment is achieved. These studies have found that mutations or copy number variations in specific genes may exhibit significant specificity, becoming one of the indicators of early carcinogenesis. The application of high-throughput sequencing technology enables us to comprehensively analyze the genetic heterogeneity of cells populations in the microenvironment, providing a profound genetic basis for the selection of potential biomarkers [247]. Secondly, the protein components in the ECM are also a key aspect of microenvironmental marker research [7]. The interaction between PCa cells and the surrounding matrix triggers changes in matrix components, including protein expression and modification. Through an in-depth study of these matrix proteins' changes, specific markers related to the PCa microenvironment can be discovered [248]. These proteins may involve key biological processes such as cells adhesion, signal transduction, and matrix remodeling, providing detailed information on the carcinogenesis process. Extracellular vesicles, as a medium for extracellular communication, also serve as a potential source of microenvironmental markers [249]. The nucleic acids, proteins, and other molecules carried by these vesicles may change the PCa microenvironment. By analyzing the composition of extracellular vesicles, specific markers related to cancer can be identified, providing new biological markers for diagnosis. Changes in metabolites are also an important direction in microenvironmental marker research [227, 250]. Metabolomic methods can reveal abnormalities in specific metabolic pathways in the PCa microenvironment, thus identifying metabolites associated with

Table 1 Extrinsic factors in TME cells and internal factors in tumor cells and their effects

Source	Category	Factors	Key points	Effects	RF
Extrinsic factors (found in TME cells)	Immune cells	T lymphocytes and subgroups	Th1 cells	Promote inflammation and improve patient prognosis	[42]
			Th2 cells	Drive tumor progression, therapeutic resistance, and castration resistance	[42]
			Treg cells	Suppress inflammatory responses and control autoimmunity	[43, 44]
			CTL cells	Recognize abnormal tumor antigens on PCa cells and target them for destruction	[45-47]
		APCs	DCs	Absorb, process, and present antigens from PCa cells	[53]
			TAMs	Enhance T cells' ability to combat PCa	[57]
			B cells	Activate T cells, resulting in a faster, more effective response	[59]
		MDSCs	PCa progression	Reduce $CD8^+$ T cells infiltration and create an immunosuppressive TME	[33]
	Angiogenic factors	VEGF family	VEGF-A	Activates signaling pathways like MAPK, PI3K/Akt and promotes angiogenesis	[79]
		FGF family	FGF1	Induces MMPs expression in PCa cells, contributing to malignant progression	[91, 92]
			FGF2	Stimulates angiogenesis and plays a role in cancer by inducing cell migration, proliferation, and differentiation	
		PDGF family	Angiogenesis	Promote cells proliferation, invasion, and metastasis	[95-98]
		Endothelial cells	Proliferation and invasion	Influence PCa cells proliferation and invasion by secreting growth factors like VEGF and MMPs	[100, 101]
	Stromal cells	CAFs	PCa growth	Promote the EMT of PCa cells and secrete growth factors that enhance angiogenesis, supplying PCa cells with nutrients and oxygen	[115-117]
		Adipocytes	Malignant adipocytes	Release significant amounts of lipid metabolites and fatty acids, providing essential energy and nutrients for PCa cells growth and metastasis	[121, 122]
	ECM	Collagen, fibronectin, elastin, and glycoproteins	ECM stiffening	Drives PCa growth, invasion, and metastasis and activates signaling pathways such as MAPK and PI3K/Akt	[125, 126]
	Cytokines and regulatory factors	TNF Family	Cells proliferation	Regulates PI3K/Akt and NF-κB activity	[183]
			Cells apoptosis	Activate JNK and MAPK	[186]
			Immune regulation and escape	Modulates activity of immune cells and immune checkpoints	[190, 191]
			Invasion and metastasis	Influence invasion and metastasis through TRAIL	[192, 193]
			Angiogenesis	Affects PCa's blood supply and growth	[194, 195]
		Transcription Factors	Regulate inflammation	NF-κB regulate various pro-inflammatory cytokines	[199, 200]
			Immune escape	NF-κB promote the expression of PD-L1	[32, 202]
			Cells cycle	Modulates CDKs and CKIs activity	[204, 205]
			Growth and invasion	Regulates genes related to angiogenesis	[65, 210, 211]
	Bacterial-mediated	Gut microbiota	Tumor immunotherapy	Reduces efficacy of PD-L1 inhibitors	[213–215]
		Ruminococcus	Gut microbiota	Phospholipid metabolism	[216, 217]
	Virus-mediated	*HPV*	The incidence of PCa	Increases average odds ratio of PCa risk	[221]
		EBV	PCa development	Exhibits notable differences in anti-apoptotic and tumor suppressor factors	[222, 223]
		HHV	The eradication of PCa stem-like cells	Enhances oncolytic herpes simplex virus effects when combined with PI3K inhibitor	[225]

Table 1 (continued)

Source	Category	Factors	Key points	Effects	RF
Intrinsic factors (found in tumor cells)	Signaling pathways	Wnt/β-catenin	PCa stem cells	Regulates self-renewal and differentiation of PCa stem cells	[159, 160]
			Infiltration and metastasis	Modulates cells adhesion and tight junctions	[154, 161]
			Immune regulation and escape	Inhibits anti-tumor immune responses and promotes immune escape	[163]
			PCa microenvironment	Alters mechanical properties and cell-cell interactions	[164]
			Angiogenesis	Promotes proliferation and migration of endothelial cells	[166]
		PI3K/Akt/mTOR	Immune evasion	Induces release of inflammatory factors	[171]
			Angiogenesis	Modulates VEGF and other molecule expressions	[83, 173]
			Drug resistance	Limits therapeutic efficacy and increases invasiveness	[174, 175]

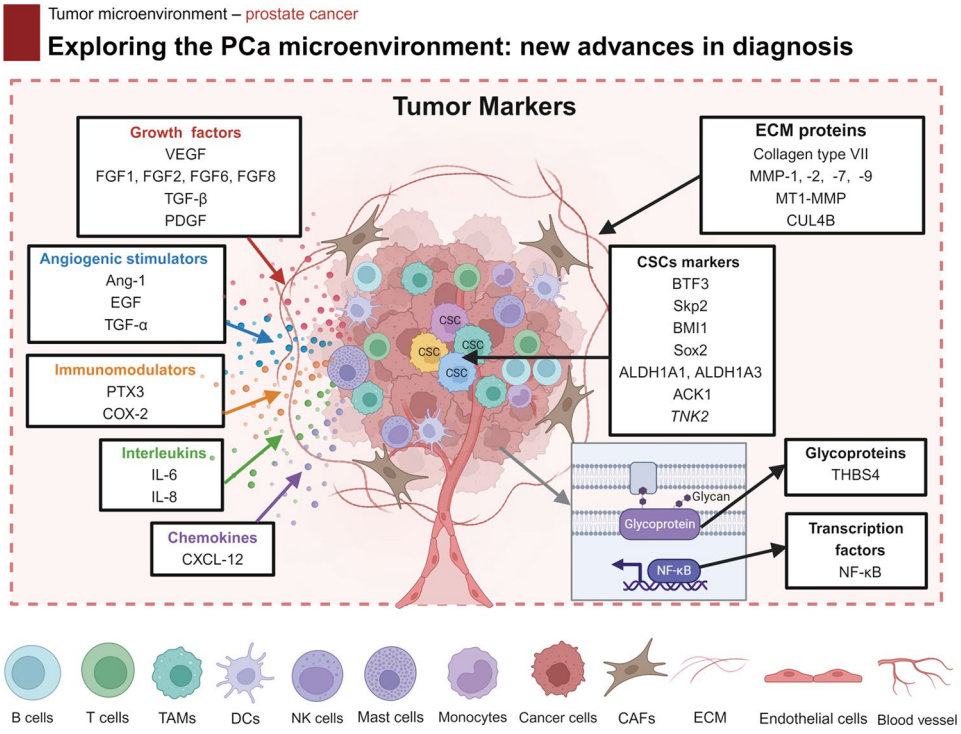


Fig. 6 Exploring the PCa microenvironment: new advances in diagnosis. The diagnosis of the PCa microenvironment involves various biomarkers, including growth factors, pro-angiogenic factors, immune mediators, IL, chemokines, ECM components, CSCs, glycoproteins, and transcription factors

cancer. These metabolites may involve key biological processes such as lipid metabolism, sugar metabolism, and amino acid metabolism, providing more precise biological markers for early diagnosis [251, 252]. Therefore, through in-depth study of these microenvironmental markers, more accurate and detailed molecular-level information can be provided for the early diagnosis of PCa, providing strong support for personalized treatment and clinical decision-making (Fig. 6).

PCa therapeutic strategies

In the section on therapeutic strategies for PCa, we highlight the importance of immunotherapy and stress the necessity of developing comprehensive treatment plans that consider the characteristics of the TME. However, the limited or absent responses seen in current PCa treatment strategies are mainly due to several factors. Firstly, the complexity and heterogeneity of the TME have a significant impact on treatment outcomes. Particularly, diverse populations of immunosuppressive cells like Treg cells and MDSCs in the PCa microenvironment hinder effective anti-tumor immune responses through the secretion of suppressive cytokines such as TGF-β and IL-10 [253, 254]. Secondly, PCa cells often exhibit high levels of the immune checkpoint molecule PD-L1, which binds to the PD-1 receptor, suppressing T cell function and enabling evasion from immune surveillance [255]. Specifically, the PD-L1/PD-1 pathway downregulates T cell activation and proliferation, reducing their cytotoxic activity and thereby diminishing the immune system's

ability to target PCa cells. This mechanism allows PCa cells to escape immune surveillance and continue to grow and metastasize within the TME. Studies have shown that PCa cells upregulate PD-L1 expression, significantly enhancing their immune evasion capabilities. This phenomenon is particularly evident in PCa patient tumor tissues, where high PD-L1 expression correlates closely with tumor progression and immune evasion [32, 256, 257]. Additionally, PCa cells can secrete various immune-suppressive factors, such as IL-10 and TGF-β, which further inhibit T cell function and promote the expansion of immune-suppressive cell populations, such as regulatory T cells. Overall, PCa cells alter immune surveillance through upregulation of PD-L1 and other immune-suppressive mechanisms, thereby facilitating persistent tumor growth and metastasis. Additionally, the presence of CSCs and the expression of multidrug resistance genes like ATP binding cassette subfamily G member 2 (*ABCG2*) and ATP binding cassette subfamily B member 1 (*ABCB1*) substantially reduce the effectiveness of current treatment strategies, as these CSCs have increased tolerance to traditional therapies and significant potential for recurrence [258]. Developing more effective combination therapy strategies presents several challenges. Firstly, optimizing combinations of various treatment modalities like immunotherapy, targeted therapy, and radiation therapy is crucial to maximize therapeutic effectiveness. For example, combining immune checkpoint inhibitors (ICIs) with anti-angiogenic therapy can overcome the limitations of single-agent therapy [259] (Fig. 7a). Secondly, overcoming immunosuppressive factors in the TME by targeting the TGF-β signaling pathway or using Treg cells inhibitors is vital to enhance anti-tumor immune responses [260, 261]. Additionally, identifying and targeting key signaling pathways such as PI3K/Akt and MAPK can enhance immune cell function while inhibiting tumor cell growth and survival [262]. Finally, developing drug delivery systems that can penetrate the barriers of the TME, such as nanoparticles and oncolytic viruses, is crucial for enhancing therapeutic effectiveness [263, 264] (Fig. 7b).

Immunotherapy has become widely recognized in recent years for its distinct mechanisms of action. However, its applicability and efficacy within the TME remain a complex and worthy topic for in-depth research [265]. To precisely tailor immunotherapy regimens, there is an urgent need to gain a deeper understanding of the PCa microenvironmental characteristics [266]. Furthermore, research should focus on the combination of immunotherapy with other treatment modalities to enhance therapeutic efficacy and reduce adverse reactions in patients. Targeting drugs against the PCa microenvironment has become one of the focal points in current cancer treatment research. The complexity of the PCa microenvironment underscores the crucial importance of designing targeted drugs. By delving into the interactions between PCa cells and their surrounding environment, it is hoped that new therapeutic targets will be discovered, leading to the development of more targeted and efficient drugs [267–270]. For example, drugs inhibiting PCa angiogenesis or targeting PCa-associated immune checkpoint molecules could potentially become integral components of future treatment strategies. The consideration of microbiota in treatment strategies is also at the forefront of current research. The interaction between gut microbiota and the immune system has profound implications on PCa development and treatment response [138]. Thus, modulating gut microbiota composition could impact patients' response to immunotherapy (Fig. 7c). For this purpose, a thorough comprehension of the roles and interconnections among various microbiota is essential for achieving targeted modulation of microbiota composition in therapeutic approaches [17]. In conclusion, insights into therapeutic strategies from the microenvironment need to comprehensively cover the potential applications of immunotherapy, drug research targeting the PCa microenvironment, and considerations of microbiota in treatment strategies, these three key areas. Through in-depth research in these aspects, it is expected that more personalized and efficient treatment methods will be discovered, leading to better clinical outcomes for PCa patients. This series of studies will provide new directions and concepts for the future development of the field of cancer treatment.

PCa clinical implications and translational potential

This review summarizes various components of the PCa microenvironment, such as immune cells, the vascular system, stromal cells, and microbiota. However, translating these findings into clinical practice requires further attention and in-depth research. Current studies mainly focus on the basic biological properties and functions of the components within the PCa microenvironment. Nonetheless, many challenges remain in effectively regulating these microenvironments in clinical settings to improve therapeutic outcomes.

Tumor cells often recruit immune cells to the tumor site to combat foreign pathogens and infections [271]. In the PCa microenvironment, however, the functions of immune cells like T cells and NK cells are often suppressed, impairing the anti-tumor immune response. Current research focuses on restoring the activity of these immune cells, with the most promising strategies being inhibitors targeting the PD-1/PD-L1 immune checkpoint. Pembrolizumab, as demonstrated in the KEYNOTE-199 trial, has shown efficacy in patients with advanced PCa. Pembrolizumab, combined with other treatments, is currently in phase III clinical trials

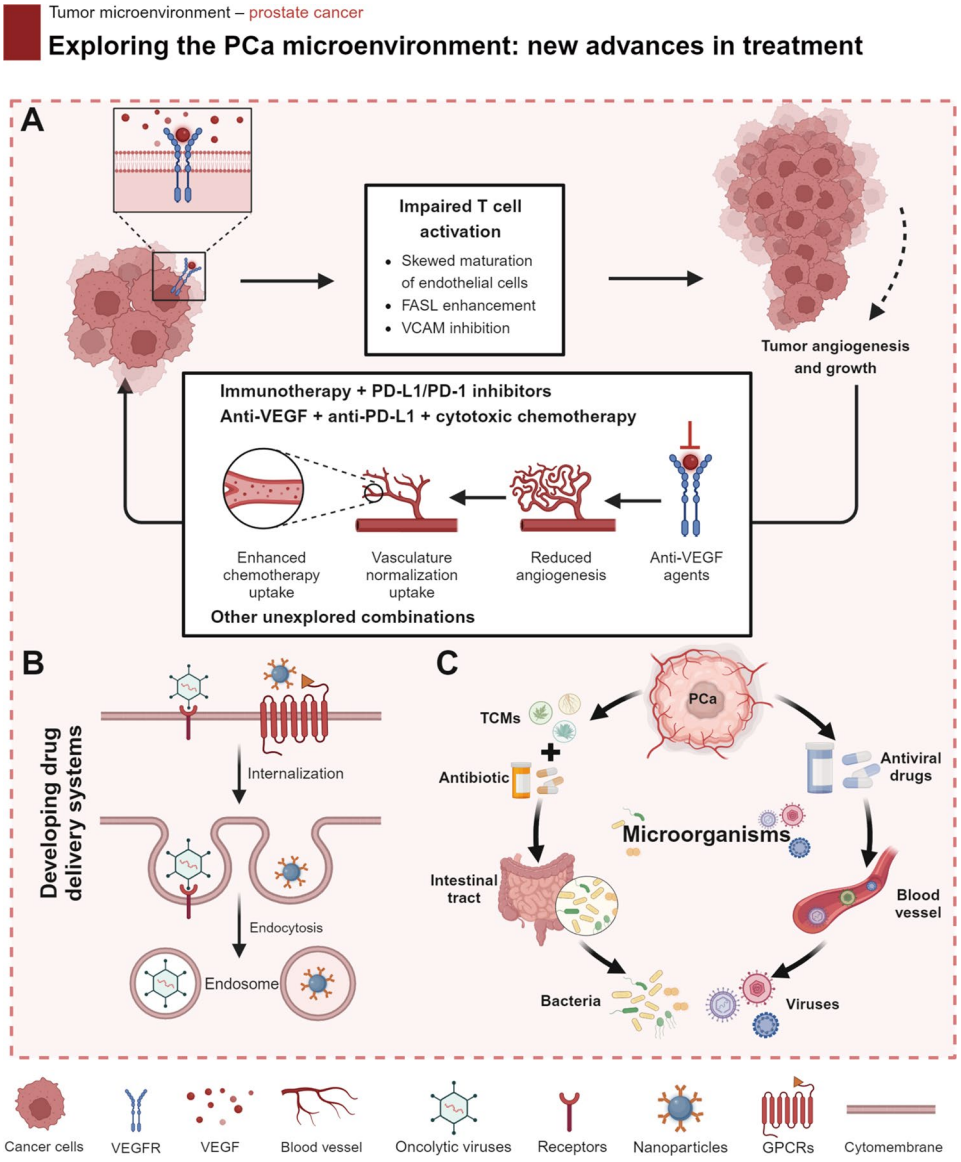


Fig. 7 Exploring the PCa microenvironment: new advances in treatment. **A** Immunotherapy strategies currently emphasize the use of PD-L1/PD-1 inhibitors in conjunction with anti-VEGF and anti-PD-L1 therapies, highlighting their increasing significance. **B** The development of drug delivery systems like nanoparticles and oncolytic viruses, capable of breaching the TME barrier, may enhance therapy effectiveness. **c**. Ongoing exploration centers on microbial therapy strategies targeting viruses and bacteria

to further improve response rates and patient survival [272–274]. Additionally, the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibitor ipilimumab and the poly ADP-ribose polymerase (PARP) inhibitor olaparib are undergoing phase III clinical trials for treating mCRPC and docetaxel-resistant diseases [275–277].

The vascular system is crucial in the PCa microenvironment. VEGF promotes tumor growth and nourishment. Anti-VEGF drugs, including bevacizumab, apatinib, pazopanib, AZD2171, and sunitinib, have demonstrated efficacy in treating PCa. Ongoing phase II clinical trials are evaluating bevacizumab for CRPC, with preliminary results showing significant potential in delaying disease progression [278]. Apatinib and pazopanib have shown promising results in phase I/II clinical trials for mCRPC [279, 280]. Vascular endothelial growth factor receptor-1 (VEGFR-1) and vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors, such as AZD2171, have shown good therapeutic effects in phase I trials for CRPC [281]. The VEGFR-2 inhibitor sunitinib is in phase II clinical trials for mCRPC [282]. Additionally, nintedanib, a drug that inhibits FGF signaling pathways, has shown potential in reducing tumor growth and metastasis in phase II clinical trials. AT-101, a lactate dehydrogenase (LDH) inhibitor, binds to and inhibits the anti-apoptotic function of Bcl-2, effectively stimulating pro-apoptotic

proteins. It has shown efficacy in PCa treatment and is currently in phase II trials for metastatic hormone-sensitive prostate cancer (mHSPC) [283–285].

Stromal cells provide critical support within the PCa microenvironment by secreting various cytokines and growth factors, promoting tumor growth and metastasis. New therapeutic strategies targeting stromal cells are being developed [286]. For example, tranilast, which inhibits the production of transforming growth factor-β1 (TGF-β1) by bone stromal cells, has shown effectiveness against metastatic CRPC. It is currently in phase II clinical trials to assess its safety and efficacy in PCa treatment [287]. Additionally, AT-101, which enhances the immune surveillance and clearance abilities of senescent fibroblasts, is in phase II clinical trials for CRPC treatment [288, 289].

The role of the microbiome in PCa progression is gaining attention. Research suggests that gut microbiota dysbiosis may influence PCa occurrence and development through immunomodulatory mechanisms. New microbiome modulation approaches to intervene in PCa are being explored. Preliminary data indicate that regulating the gut microbiota can enhance the immune response and improve treatment outcomes [290]. For example, the antibiotic cocktail therapy ABX, which reduces short-chain fatty acid (SCFA) production by gut microbiota and lowers insulin-like growth factor-1 (IGF-1) levels, is in phase III clinical trials for CRPC and shows improved treatment outcomes [291, 292]. Additionally, vaccination plays a significant role in PCa clinical treatment. The peptide viral vaccine PROSTVAC-V/F, which inhibits PD-1, has shown efficacy in inhibiting the progression of metastatic CRPC and is now in phase III clinical trials [293, 294]. The prostate acid phosphatase DNA vaccine (pTVG-HP) has shown efficacy in phase II trials for hormone-sensitive prostate cancer (HSPC) [295]. Sipuleucel-T, a monocyte-based cancer vaccine, is the only FDA-approved therapeutic vaccine for PCa and is a treatment option for asymptomatic and minimally symptomatic patients in North America. It is currently in phase II trials for CRPC [296, 297] (Table 2).

Moreover, identifying predictive biomarkers for immunotherapy response is critical for improving the diagnosis and treatment of PCa. Current biomarkers that may influence the efficacy of immunotherapy in PCa include genetic-based markers such as tumor mutational burden (TMB), microsatellite instability/mismatch repair (MSI/MMR), and cyclin-dependent kinase 12 (CDK12) mutations, along with cell type proportion markers like the

Table 2 PCa clinical implications and translational potential

PCa microenvironment	Drug	Pathological stage	Phase	Mechanisms	RF
Immune cells	Pembrolizumab	mCRPC	II / III	Inhibits PD-1, enhancing T cell activity and boosting anti-tumor immune response	[272, 273]
	KEYNOTE-199	mCRPC	II	Inhibits PD-L1, preventing its binding to PD-1, restoring T cell function	[274]
	Ipilimumab	mCRPC	II / III	Inhibits CTLA-4, increasing T cell proliferation and anti-tumor activity	[275]
	Olaparib	mCRPC	III	Inhibits PARP, leading to incomplete DNA repair in tumor cells, resulting in cell death	[276, 277]
Vascular system	Bevacizumab	CRPC	II	Inhibits VEGFR tyrosine kinase activity, blocking tumor angiogenesis	[278]
	Apatinib	mCRPC	I / II	Inhibits VEGFR tyrosine kinase activity, blocking tumor angiogenesis	[279]
	Pazopanib	mCRPC	II	Inhibits VEGFR tyrosine kinase activity, blocking tumor angiogenesis	[280]
	AZD2171	CRPC	I	Inhibits VEGFR-1 and VEGFR-2, suppressing tumor angiogenesis	[281]
	Sunitinib	mCRPC	II	Specifically inhibits VEGFR-2, blocking tumor angiogenesis	[282]
	AT-101	mHSPC	II	Inhibits LDH, tumor cell contraction and ATP synthesis, tumor cell growth	[283-285]
	Nintedanib	mCRPC	II	Targets FGF signaling pathways, inhibiting tumor growth and angiogenesis	[286]
Stromal cells	Tranilast	CRPC	II	Inhibits TGF-β1 production, reducing tumor-associated fibrosis and immune suppression	[287]
	AT-101	CRPC	II	Eliminates senescent fibroblasts, improving the TME and enhancing anti-tumor response	[288, 289]
Microbiota	ABX	CRPC	III	Inhibits fatty acid transport proteins, reducing fatty acid uptake by tumor cells and inhibiting tumor growth	[291, 292]
	PROSTVAC-V/F	mCRPC	III	Inhibits PD-1, enhancing T cell activity and boosting anti-tumor immune response	[293, 294]
	pTVG-HP	HSPC	II	/	[295]
	Sipuleucel-T	CRPC	II	Modulates PAP, affecting PCa cells metabolism and proliferation	[296, 297]

neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) [298–301].

In recent years, TMB has gained significant attention as a biomarker in ICI research. Research indicates that PCa patients with high TMB are more likely to benefit from ICI therapy. Tumors with high TMB typically express numerous abnormal proteins, which are displayed on the surface of tumor cells and recognized by immune cells, thereby triggering an immune response [302]. A large retrospective study in advanced PCa showed that patients with TMB ≥ 10 mutations per megabase (mt/Mb) experienced prolonged time to next treatment and significantly improved overall survival following ICI therapy, compared to those receiving taxane chemotherapy [303].

Mismatch repair deficiency (dMMR) results from the loss of any mismatch repair protein, leading to the accumulation of errors during DNA replication and ultimately causing MSI. Tumors with high microsatellite instability (MSI-H)/dMMR often show increased T-cell infiltration, making them more responsive to ICIs [304, 305]. In a study by Abida et al., 6 out of 11 mCRPC patients with MSI-H/dMMR exhibited a significant decline in prostate-specific antigen (PSA) levels following ICI treatment [306].

Loss of CDK12 disrupts DNA damage repair, leading to increased gene fusions, a higher neoantigen load, and enhanced T-cell infiltration. Several studies have reported that PCa patients with CDK12 mutations are more likely to respond to ICIs. Wu et al. observed that 2 out of 4 mCRPC patients with biallelic CDK12 inactivation responded positively to PD-1 inhibitor monotherapy [307]. Similarly, Antonarakis et al. found that 3 out of 9 mCRPC patients with CDK12 mutations achieved partial responses after treatment with nivolumab [308].

A meta-analysis of 7,228 PCa patients found that elevated NLR and PLR were associated with poor prognosis, suggesting their potential as prognostic biomarkers. However, the mechanisms underlying the relationship between elevated NLR/PLR and adverse outcomes in PCa remain unclear and require further investigation [309].

Conclusion and perspective

PCa stands out as one of the prevailing male malignancies, commanding widespread attention due to its profound impact on public health. As medical technology advances at a rapid pace, the intricate landscape of the PCa microenvironment has emerged as a focal point for comprehensive investigation. Delving into the microenvironment of PCa unveils a labyrinthine network system characterized by its complexity and multi-level interactions. Comprising immune cells, angiogenic factors, stromal cells, and an array of molecular signaling pathways, among other constituents, this milieu offers a rich tapestry of avenues for unraveling the mechanisms underlying PCa pathogenesis and progression. The microenvironment of PCa serves as a dynamic arena wherein myriad cellular and molecular players orchestrate a delicate balance between tumor suppression and promotion. Understanding the interplay between these elements holds promise for the development of novel therapeutic modalities and preventive strategies aimed at mitigating the burden of PCa. Notably, insights gleaned from dissecting the PCa microenvironment have the potential to revolutionize existing paradigms in cancer treatment, fostering tailored approaches that capitalize on the unique vulnerabilities of the tumor milieu. While the precise determinants driving the high incidence of PCa remain incompletely elucidated, a constellation of factors, including environmental exposures, genetic predispositions, and lifestyle variables, have been implicated in shaping the risk landscape of this disease. Unraveling the intricate interplay between these factors and their influence on the PCa microenvironment represents a critical frontier in the quest to curtail the burgeoning burden of this disease. In essence, the exploration of the PCa microenvironment transcends the confines of traditional oncological research paradigms, heralding a new era characterized by precision medicine and personalized interventions tailored to the unique molecular landscape of individual tumors. By deciphering the intricacies of the PCa microenvironment, researchers stand poised to forge innovative therapeutic strategies that hold the promise of transforming the management of this formidable disease entity.

This review comprehensively summarized the role of the microenvironment in PCa, focusing on the specific background of PCa, and providing in-depth analysis of immune cells, angiogenesis, and molecular mechanisms. This not only helps to comprehensively understand the pathogenesis of PCa but also provides rich ideas for future treatments. Based on this, further exploration of the unique characteristics of the PCa microenvironment is warranted. The role of immune cells in the PCa microenvironment, including different subsets of T lymphocytes and their functions, as well as the crucial role of APCs, is carefully analyzed. The relationship between angiogenesis and PCa, including the regulation of the VEGF family and the complex interaction between endothelial cells and cancer cells, reveals the delicate balance between PCa growth and blood supply. The functions of stromal cells, especially the synergistic effects of CAFs and stromal cells, and the impact of ECM changes on PCa development, are elaborated in this review, focusing on molecular mechanisms research. The role of signaling pathways in the PCa microenvironment, with particular emphasis on the regulatory mechanisms of the Wnt/β-catenin and PI3K/Akt signaling pathways, is explored.

The importance of cytokines and regulatory factors, especially the role of the TNF family and transcription factors in the regulation of the PCa microenvironment, uncovers mysteries at the molecular level. An in-depth exploration of the potential clinical applications of the PCa microenvironment reveals the impact of the microenvironment on PCa diagnosis, including the potential application of microenvironmental biomarkers, providing clinicians with more precise diagnostic tools. Insights into treatment strategies from the microenvironment, including the potential application of immunotherapy and targeted drug research on the PCa microenvironment, provide new directions for future treatments. Reviewing the challenges in the current research field of PCa microenvironment and the development of new technological methods, it becomes evident that addressing technical limitations and theoretical challenges necessitates collaborative efforts to achieve breakthroughs.

We have noticed that there are still some challenges in the clinical translation and application of PCa microenvironment research. Although we have mentioned several microenvironment biomarkers, their accuracy, specificity, and clinical predictive value still need further validation in clinical practice. Additionally, a deeper understanding of the interactions among various biomarkers in the microenvironment needs to be strengthened, which will help reveal more details about the complexity of the TME. Firstly, in current PCa microenvironment research, we must recognize that there are some challenges. For example, in terms of clinical translation, although we have identified multiple microenvironment biomarkers, their accuracy and specificity have not been fully validated in clinical practice. Furthermore, the existing research lacks a thorough understanding of the interactions among various biomarkers in the microenvironment, leading to a need for a more comprehensive understanding of the complexity of the TME. In response to these challenges, we propose several future research directions: ①Establishment of biomarker combination models: develop combination models for different PCa subtypes and clinical stages, combining multiple microenvironment biomarkers to improve diagnostic and predictive accuracy. ②Application of bioinformatics and artificial intelligence in microenvironment analysis: utilize bioinformatics and artificial intelligence technologies to delve into microenvironment data, discover new biomarkers, signaling pathways, and their clinical significance. ③Research on microenvironment-regulated treatment strategies: explore treatment strategies targeting the microenvironment, such as targeted therapy for specific biomarkers, immunomodulatory therapy, etc., to achieve more precise personalized treatment. ④Exploration of precise treatment strategies for microenvironment regulation: explore precise treatment strategies targeting the microenvironment, such as targeted therapy for specific biomarkers, immunomodulatory therapy, etc., to achieve personalized treatment and improve treatment effectiveness. ⑤Multi-center large-sample clinical validation studies: conduct multi-center, large-sample clinical validation studies to verify the feasibility and effectiveness of new biomarkers or models in clinical practice, thereby accelerating their clinical application. ⑥Precision medicine perspective: advocate starting from the perspective of precision medicine, combining personalized treatment strategies and microenvironment characteristics, develop biomarker combination models suitable for different patients, and apply them in clinical practice. ⑦Prospective clinical research: we advocate for prospective, multi-center clinical research to validate the feasibility and effectiveness of new biomarker combination models in different clinical scenarios, providing more reliable evidence for personalized treatment. Exploring these future research directions will provide a more comprehensive and in-depth understanding of PCa microenvironment research, promote the clinical application of microenvironment biomarkers, and lay a more solid scientific foundation for personalized treatment and precision medicine in PCa.

Abbreviations

AAC	Amino acid chain
ABCB1	ATP binding cassette subfamily B member 1
ABCG2	ATP binding cassette subfamily G member 2
ACK1	Activated CDC42 kinase-1
ADT	Androgen deprivation therapy
Akt	Protein kinase B
ALDH1A1	Aldehyde dehydrogenase 1A1
ALDH1A3	Aldehyde dehydrogenase 1A3
Ang-1	Angiopoietin-1
APCs	Antigen-presenting cells
AR	Androgen receptors
ATG5	Autophagy-related gene 5
bFGF	Basic fibroblast growth factor
BMI1	B lymphoma Mo-MLV insertion region 1
BTF3	Basal transcription factor 3
CAFs	Cancer-associated fibroblasts
CD28	Cluster of differentiation 28
CD31	Cluster of differentiation 31
CD40	Cluster of differentiation 40
CD40L	Cluster of differentiation 40 ligand
CD80	Cluster of differentiation 80
CD86	Cluster of differentiation 86
CDKs	Cyclin-dependent kinases
CDK12	Cyclin-dependent kinase 12
CKIs	Cyclin-dependent kinase inhibitors
COX-2	Cyclooxygenase-2
CRPC	Castration-resistant prostate cancer
CSCs	Cancer stem cells
CTL	Cytotoxic $CD8^+$ T lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen-4
CUL4B	Cullin 4B
CXCL-12	C-X-C motif chemokine ligand-12
DCs	Dendritic cells
dMMR	Mismatch repair deficiency
EBV	Epstein-barr virus
ECM	Extracellular matrix
EGF	Epidermal growth factor
EMT	Epithelial-mesenchymal transition

Fas	Factor associated suicide
FasL	Factor associated suicide ligand
FGF	Fibroblast growth factor
FGF1	Fibroblast growth factor 1
FGF2	Fibroblast growth factor 2
FGF6	Fibroblast growth factor 6
FGF8	Fibroblast growth factor 8
FGFR	Fibroblast growth factor receptor
GPCRs	G protein-coupled receptors
HHV	Human herpes virus
HPV	Human papilloma virus
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type-1
HSV-2	Herpes simplex virus type-2
ICI	Immune checkpoint inhibitor
ICIs	Immune checkpoint inhibitors
IFN-γ	Interferon-γ
IGF-1	Insulin-like growth factor-1
IL	Interleukin
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-7	Interleukin-7
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-15	Interleukin-15
IL-23	Interleukin-23
IL-30	Interleukin-30
LDH	Lactate dehydrogenase
M2-MΦ	M2-macrophages
MAPK	Mitogen-activated protein kinase
mCRPC	Metastatic castration-resistant prostate cancer
mDCs	Myeloid dendritic cells
MDSCs	Myeloid-derived suppressor cells
MHC-I	Major histocompatibility complex-I
MHC-II	Major histocompatibility complex-II
MMP-14	Matrix metalloproteinase-14
MMP-2	Matrix metalloproteinase-2
MMP-3	Matrix metalloproteinase-3
MMP-7	Matrix metalloproteinase-7
MMP-9	Matrix metalloproteinase-9
MMPs	Matrix metalloproteinases
MMR	Mismatch repair
MSI	Microsatellite instability
MSI-H	High microsatellite instability
MT1-MMP	Membrane type 1-matrix metalloproteinase
mTOR	Mechanistic target of rapamycin kinase
MUC1-C	Mucin 1-C
mt/Mb	Mutations per megabase
NFs	Normal fibroblasts
NF-κB	Nuclear factor-kappa B
NLR	Neutrophil-to-lymphocyte ratio
NK	Natural killer
PARP	Poly ADP-ribose polymerase
PCa	Prostate cancer
PD-1	Programmed cell death protein-1
pDCs	Plasmacytoid dendritic cells
PDGF	Platelet-derived growth factor
PD-L1	Programmed cell death-ligand 1
PECAM-1	Platelet endothelial cell adhesion molecule-1
PGE_2	Prostaglandin E_2
PI3K	Phosphoinositide 3-kinase
PLGF	Placental growth factor
PLR	Platelet-to-lymphocyte ratio
PSA	Prostate-specific antigen
pTVG-HP	Prostate acid phosphatase DNA vaccine
PTX3	Pentraxin 3
Rb	Retinoblastoma
RBCs	Red blood cells
SCFA	Short-chain fatty acid
Skp2	S-phase kinase associated protein 2
SNs	Sentinel lymph nodes
Sox2	Sex determining region Y-box 2
TAMs	Tumor-associated macrophages
TCMs	Traditional Chinese medicines
TCR	T cell receptor
TGF-α	Transforming growth factor-α
TGF-β	Transforming growth factor-β
TGF-β1	Transforming growth factor-β1
Th	Helper $CD4^+$ T
THBS4	Thrombospondin 4
TIMo	Tumor-inflammatory monocytes
TLR	Toll like receptor
TME	Tumor microenvironment
TMB	Tumor mutational burden
TNF	Tumor necrosis factor
TNF-α	Tumor necrosis factor-α
TNF-β	Tumor necrosis factor-β
TNK2	Tyrosine kinase non receptor 2
TRAIL	TNF-related apoptosis-inducing ligand
Treg	Regulatory $CD4^+$ T
TYR	Thyrosinase
UBE2C	Ubiquitin conjugating enzyme complex
VCAM	Vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor-A
VEGF-B	Vascular endothelial growth factor-B
VEGF-C	Vascular endothelial growth factor-C
VEGF-D	Vascular endothelial growth factor-D
VEGFR	Vascular endothelial growth factor receptor
VEGFR-1	Vascular endothelial growth factor receptor-1
VEGFR-2	Vascular endothelial growth factor receptor-2

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Authors' contributions
Lin Chen: investigation, writing original-draft, drawing. Yu-Xin Xu: drawing, check. Yuan-Shuo Wang: writing original-draft, table. Ying-Ying Ren: writing original-draft, check. Xue-Man Dong: writing original-draft. Pu Wu: writing original-draft. Tian Xie, Qi Zhang, Jian-Liang Zhou: conceptualization, project administration, writing-review & editing.

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